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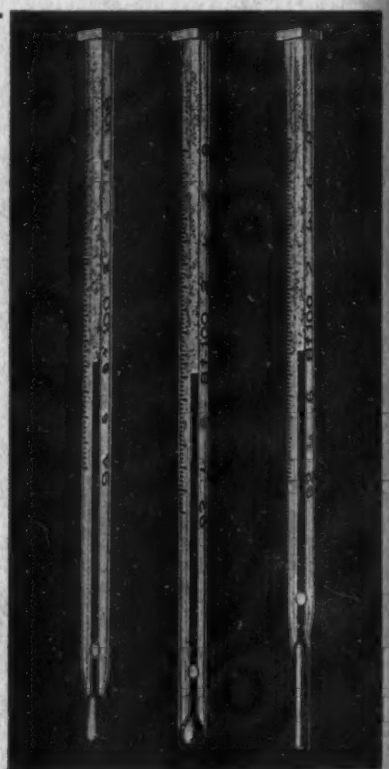

SILICO-TUBERCULOSIS[1]

OSCAR AUERBACH AND MARGUERITE G. STEMMERMAN

The literature of the past two or three decades has presented a picture of silico-tuberculosis, in which the phthisis is described as unique and as an important factor in the development of the silicotic nodule. Since, from a study of our autopsy material, we have been unable to confirm either of these special qualities of tuberculosis in the lung of the silicotic, a description of our findings seemed indicated.

It is the purpose of this report, therefore, to correlate the clinical and pathological findings of our cases of silico-tuberculosis and to compare these findings with those in patients succumbing to chronic pulmonary tuberculosis without silicosis. In a previous study (1), based on 12 cases, we were impressed by the fact that the pulmonary tuberculosis was altered quantitatively, but not qualitatively by the presence of pneumonoconiosis. We have at this time also tried to determine how these quantitative differences, as well as the qualitities of the silicotic process itself, influence collapse therapy.

MATERIAL

In the course of our routine necropsy examinations, which is almost exclusively upon patients with tuberculosis, we have found 63 cases of silicosis, 54 of whom had an associated chronic pulmonary tuberculosis. The presence, in a tuberculosis institution, of 9 (14 per cent) silicotics in whom careful histological examination failed to reveal any evidence of tuberculous tissue is interesting in view of the statement of Beattie (2) that over 90 per cent of all silicotics succumb to tuberculosis. This 14 per cent represents those cases which were admitted to a tuberculosis institution with a mistaken diagnosis of phthisis.

This study will concern itself only with the 54 cases of silico-tuberculosis. The clinical and pathological findings in this group will be compared with those in 200 unselected cases of chronic pulmonary tuberculosis. In order to obtain a group comparable to the silicotics, only adult males over the age of twenty years are included in the unselected cases.

Age: From table 1-A, a number of differences can be seen in the silicotic and unselected groups. Only 9 (16.6 per cent) of the silicotics developed pulmonary tuberculosis in the third and fourth decades; whereas in the nonsilicotic group, 91 (45.5 per cent) occurred in this age group. The majority of cases, 35 (64.8 per cent), with silico-tuberculosis were between forty and fifty-nine years; whereas in the nonsilicotic, chronic pulmonary tuberculosis appeared predominantly one decade earlier, between the ages of thirty and forty-nine years, 101 cases (50.5 per cent).

Race: Forty of the 54 individuals (74 per cent) were white, while 14 (26 per cent) were Negroes. This is approximately the same ratio of whites (70 per

[1] From the Department of Pathology, Sea View Hospital, Staten Island, New York.

cent) to Negroes (30 per cent) in the unselected cases of chronic pulmonary tuberculosis. The number of Negroes with silicosis in our series is higher than in most reports, probably because a large number of these persons contracted silicosis working in our city subways, where many of this race are so employed.

Occupation: It has been stated frequently that the type of pneumonoconiosis which develops in certain industries (sandstone cutters, granite cutters, potters) has a greater tendency to develop chronic pulmonary tuberculosis than in others (soft coal miners, limestone masons, brickmakers). Our series cannot decide this point because the persons in our community come chiefly from industries in the eastern part of the United States. As may be seen from table 2 there were

TABLE 1

Comparison of silico-tuberculosis and non-silico-tuberculosis

Age.....	20–29 yrs.	30–39 yrs.	40–49 yrs.	50–59 yrs.	60–69 yrs.	70–79 yrs.	
A	3 5.6%	6 11%	17 31.5%	18 33.3%	7 13%	3 5.6%	Silico-tuberculosis
	39 19.5%	52 26%	49 24.5%	38 19%	21 15.5%	1 0.5%	Non-silico-tuberculosis
Duration of tuberculosis.....	12 m or less	13–24 m	2.5–3 yrs.	3–4 yrs.	5–6 yrs.	7 yrs. or more	
B	18 33.4%	19 35.2%	5 9.2%	6 11.1%	1 1.9%	5 9.2%	Silico-tuberculosis
	69 34.5%	45 22.5%	13 6.5%	33 16.5%	19 9.5%	21 10.5%	Non-silico-tuberculosis
Location of cavities ...	RUL	LUL	RLL	LLL	RML	Perforated fissure	
C	37 69.8%	43 81%	29 54.7%	27 51%	10 19%	11 20%	Silico-tuberculosis
	166 83%	158 79%	81 40.5%	94 47%	39 19.5%	29 14.5%	Non-silico-tuberculosis

46 persons who were known to have been employed in specific dusty trades. In those instances in which the worker had been engaged in more than one type of industry, the recorded occupation is the one in which he had worked longest. The greatest number of cases of pulmonary tuberculosis were among the rock drillers and coal miners. Twelve patients were recorded as having been coal miners, in 5 of whom it was noted that the occupation was that of hard coal mining. In the other 7 cases no statement was made whether the person had been a hard or soft coal miner. The 17 (37 per cent) rock drillers had all been engaged in subway construction in New York City. Willis (3) has noted that the incidence of pneumonoconiosis among this group of workers is higher than

commonly believed, due to the high proportion of total (56 to 95 per cent) and free silica (1 to 84 per cent) in the rock of New York. Even intermittent employment for short periods has been found to be hazardous.

In 8 of the 54 cases there was no record of an occupational history. This is accounted for by three factors. In some cases the presence of chronic pulmonary tuberculosis so altered the picture of pneumonoconiosis that when the patient was admitted to the hospital there was no suspicion of silicosis and the patient was not thoroughly questioned about his occupation. In a few cases the patients were admitted in so critical a condition that close questioning was impossible. In the third group, the patients had apparently been exposed to a dusty trade many years before the onset of pulmonary tuberculosis. While the occupational history did not disclose such a trade in the years immediately preceding admission, a complete work history of the patient would certainly have revealed the silicosis-producing occupation. In a number of instances the history of

TABLE 2

Occupations

STONE CUTTER	COAL MINER	FOUNDRY WORKER	ROCK DRILLER	METAL POLISHER	GRAPHITE MINER	CLEANSING POWDER	GOLD MINER	IRON ORE MINER	SAND BLASTER
5(11%)	12(26%)	4(8.6%)	17(37%)	1(2.2%)	1(2.2%)	1(2.2%)	1(2.2%)	1(2.2%)	3(6.4%)

TABLE 3

Length of exposure to dusty trade

1–2 YEARS	3–4 YEARS	5–9 YEARS	10–14 YEARS	15–19 YEARS	20 OR MORE YEARS
7 (18%)	3 (8%)	7 (18%)	7 (18%)	7 (18%)	8 (20%)

exposure was elicited from the family after the discovery of pneumonoconiosis at autopsy.

Length of exposure: Table 3 indicates that in 39 cases, where the length of exposure was recorded, it varied from one year to over twenty years. When the length of exposure was under two years there was little correlation between this factor and the extent of the pneumonoconiosis, 4 in this group having moderate, 2 minimal, and one marked silicotic involvement. When the exposure was of twenty or more years' duration, there was a closer correlation, the silicosis in 5 being of marked and in 3 being of moderate extent.

Onset of tuberculosis following the exposure to dust: Table 4 records in 40 cases the period at which tuberculosis developed in relation to the time of exposure to dust. It is interesting to observe that tuberculosis developed while they were working in the dusty trades in 13 cases. The majority of persons, however, developed their tuberculosis from two to more than twenty years following the cessation of exposure to dust.

Duration of chronic pulmonary tuberculosis: Table 1-B reveals that the ma-

jority of patients (77.8 per cent) died within two and one-half years after the onset of pulmonary tuberculosis. In the unselected group 63.5 per cent died during this period, an observation which indicates that chronic pulmonary tuberculosis in the presence of silicosis runs a course not unlike that of pulmonary tuberculosis without silicosis. Our findings do not support the statement made by Ickert (4) that silico-tuberculosis, being an indurative form of tuberculosis, runs a more chronic course, the patients expectorating tubercle bacilli for many years. He believes that the rule that individuals with open tuberculosis in general survive only two and one-half years, does not hold for dust workers.

TABLE 4

Cessation of exposure before onset of tuberculosis

ONSET WHILE WORKING	2 YRS.	3–5 YRS.	6–9 YRS.	10–14 YRS.	15–19 YRS.	20 YRS.	MANY YEARS
13 (32.5%)	2 (5%)	7 (17.5%)	6 (15%)	6 (15%)	2 (5%)	1 (2.5%)	3 (7.5%)

PATHOLOGY

Pneumonoconiosis: The gross and microscopical character of pneumonoconiosis has been described so frequently and so adequately that it bears no repetition here.

Silico-tuberculosis: In one of our cases the silicosis was associated with a miliary dissemination throughout both lungs. This was the result of an acute generalized miliary seeding from a urogenital tuberculosis. The miliary seeding was similar to that seen in nonsilicotic lungs, the foci being larger and more numerous in the apical and ventral aspects, decreasing in size and intensity toward the base. The smallest foci were present in the posterior and basal aspects of both lower lobes.

The remaining 53 cases showed evidence of chronic pulmonary tuberculosis, the presence of silicosis altering the picture of chronic pulmonary tuberculosis to only a slight degree. Our findings do not substantiate the views of Ickert (4) that the presence of silicosis greatly changes the character of chronic pulmonary tuberculosis. Ickert goes so far as to state that, inasmuch as tuberculosis in pneumonoconiosis is predominantly productive in character, there is justification for speaking of "a special type of pulmonary tuberculosis" and he gives it the name of *Staublungentuberkulose.*

In all of our 53 cases the silicosis and the tuberculosis could always be distinguished as two separate and independent processes. In no instance did we find evidence to support the view of Huebschmann and Ickert (4) that in the great majority of cases the silicotic foci are the result of the inhalation of dust combined with tubercle bacilli.

Nor do our findings confirm the views of Simson, Strachan and Irvine (5) that the massive fibrosis in silicosis is usually the result of the tuberculous infection. This massive involvement they have termed "tuberculo-silicosis." Simson

points out that in this type there may be no definite histological evidence of tuberculosis beyond the suggestive indication of necrotic degeneration of the central portions of the silicotic nodules. Their proof of the tuberculous character of these foci rests on the fact that many of these lesions in the lungs as well as the hilar lymph nodes produced tuberculosis in inoculated animals.

We find it difficult to understand why the tubercle bacillus, which, invading the body under ordinary circumstances, sets up a typical tuberculous reaction, should fail to do so when inhaled along with dust particles. One might argue that our material deals only with the type which this group of authors called "silicosis with tuberculosis." Yet 13 of the individuals in our series developed tuberculosis while they were working and presumably inhaling dust and bacilli concomitantly. All 13 cases showed typical chronic pulmonary tuberculosis which was similar, grossly and histologically, to the other 40 in the series.

Unlike Gardner (6), we have been unable to find any evidence of tubercles on microscopical examination within these areas of massive fibrosis, in spite of examining large areas of the tissue, although tuberculous foci bordering the fibrosis are not unusual. We agree with Gardner (6) and Vorwald (7), however, that the cavities filled with inky fluid are the result of an ischaemic necrosis due to an obliterative endarteritis. The necrosis in the central portions of the nodules is probably the beginning of these cavities.

Although the character of chronic pulmonary tuberculosis is similar in all cases, the extent of the process is to a great degree dependent upon the amount of silicosis present. Generally, we found the most extensive tuberculosis in those cases in which we classified the silicosis as minimal or moderate.

In the course of chronic pulmonary tuberculosis we find three characteristic tuberculous lesions: (*1*) caseous lobular pneumonia, (*2*) the cavity and (*3*) acinous-nodose foci. The areas of caseous lobular pneumonia may cavitate, following central liquefaction, or may heal with the development of an encapsulated caseous focus. As healing progresses calcium may be deposited in the caseous foci. In occasional instances the central zone of caseation may be completely replaced by hyalinized connective tissue. It is these foci which may simulate silicotic nodules (Gardner (8)). The acinous-nodose focus, a predominantly productive lesion, when healed results in fibrosis with surrounding areas of emphysema. Acinous-nodose foci are very infrequently observed in silico-tuberculosis.

Tuberculous lobular pneumonia: Tuberculous bronchopneumonia develops in the intervening lung parenchyma between the silicotic foci. The pneumonic zone is of variable extent and is frequently located in the vicinity of the silicotic foci. The caseation extends to the foci and may even completely convert them into caseous material. However, in these instances the original area of caseation is still distinguishable from the necrotic focus. In the silicotic focus, the elastic fibres are destroyed, whereas in the caseous pneumonic area, an exudative process, the elastic fibres of the underlying lung parenchyma are clearly discernible with the elastica-van Gieson stain.

This exudative caseous pneumonia which was a constant finding in our 53

cases is in direct contrast to the findings of Gardner (9). He stated that the tuberculous lesions surrounding the silicotic foci usually are of a productive type, consisting of a cellular granulation tissue which shows a marked tendency toward organization. We have found a productive reaction, but it is located at the periphery of the caseous pneumonia, only, in the form of a vascular granulation tissue.

Liquefaction of the caseous pneumonia results in the formation of a cavity. If, within this pneumonic area, there is a silicotic focus which has not been completely converted into caseation, the liquefaction will result in its being loosened from its mooring and expectorated, along with the liquefied caseous material. The expectorated particles are stony hard, gray, or gray-black, in consistency and color. Microscopically, they may show evidence of caseation. The whorl arrangement of the fibres is clearly seen and the nodules are laden with black pigment.

The cavity—location: From table 1–C it may be seen that cavities are slightly more frequent in the lower lobes in the patients with silico-tuberculosis than in those with simple chronic pulmonary tuberculosis without silicosis. This agrees with the findings of Vorwald (7). Our studies do not agree with his observations that there is a predilection toward localization in the mid-portion and lower portion of each lobe of the silicotic lung, nor with Gardner (9) that tuberculosis is more common in the middle or lower lung. The cavities in the upper lobes, in the vast majority of instances, develop in the postero-lateral aspect of the upper lobe, 2 to 3 cm. above the base of the lobe, a location which is similar to that in nonsilicotic chronic pulmonary tuberculosis. Cavities in the lower lobes are almost universally present in the apical portions. In some instances, the cavities are more basally and centrally located, but this may also be true in the nonsilicotic cases. However, the cavities in silico-tuberculosis, as in simple chronic pulmonary tuberculosis, develop chiefly in the upper lobes. The greater incidence of lower lobe cavities in silico-tuberculosis may be due to the fact that there is a greater proportion of acute cases in this group, over three-fourths succumbing within two and one-half years. Yet, the number of cavities per case is approximately the same in the silicotic and nonsilicotic groups, 2.9 and 2.6 excavations per lung, respectively.

Size and shape: The size of the cavities varied from 5 mm. to 9 cm. in their largest diameters. This is similar to nonsilicotic pulmonary tuberculosis. In 11 instances (20 per cent) the cavity in the upper lobe extended through the interlobar fissure into the lower lobe. Although the extension through the fissure is more frequent than in nonsilicotic pulmonary tuberculosis (14.5 per cent), it is not as frequent as we assumed in our previous study (1). We feel that the somewhat greater frequency of perforation of the fissure is attributable to the fact that among the silicotics it is much less often obliterated by the connective tissue, which acts as a barrier to the extension of the cavity.

The shape of the cavity, like those of chronic pulmonary tuberculosis, is oval and round. We feel that although the destruction of pulmonary tissue leads to the irregularly shaped, partially collapsed cavity of the postmortem

table, the oval and round contour is maintained during life by the presence of air within the excavation. The sphericity, as well as the size of the cavity, will then depend upon the volume of contained gases. If the bronchial orifices are so occluded by granulation tissue or debris that air is permitted ingress but not egress, its sphericity and diameters will be limited during life only by the elasticity of its walls and the surrounding lung tissue.

Physical characteristics: The tuberculous cavity in uncomplicated cases of chronic pulmonary tuberculosis is characterized by an inner wall, which in some regions is dirty gray (pyogenic), in other areas yellow (caseous). Beyond this, there is a narrow red zone of vascular granulation tissue which, although although always present on microscopical examination, is usually only distinguishable on gross study in fresh cavities. This granulation tissue is followed in turn by a gray zone of connective tissue, resulting from the organization of the perifocal inflammation. As the cavity grows older this zone of connective tissue becomes wider and accumulating coal pigment becomes gray-black. The presence of obliterated pulmonary arteries, which traverse the cavity as trabeculae, and patent bronchial orifices complete the typical cavity.

Our studies have led us to the conclusion that silicosis only alters the picture of chronic pulmonary tuberculosis in that, by its presence, it forms a barrier to the full development of the tuberculous process, which it limits, but never completely changes. We have found no histological confirmation of the statement that there is a different type of tuberculosis when silicasis is present. As we have stated above the tuberculous cavity has its origin in a tuberculous lobular pneumonia. After the tubercle bacilli invade the lung, the tuberculous process develops in the alveolar spaces. In nonsilicotic lungs, since there are no barriers, the process develops completely. This is not so in silicotic lungs, and this becomes more apparent, the more extensive the silicosis.

The tuberculous lobular pneumonia develops in areas of well aerated lung parenchyma. It is surrounded by a zone of tuberculous vascular granulation tissue, which is in turn followed by the perifocal inflammation. The latter is converted into fibrous tissue to form the wall of the cavity, after the central zone of caseation has been liquefied and expectorated. Frequently, in silico-tuberculosis, the inner wall of the cavity is lined by a zone of caseation or a pyogenic membrane in only a part of its circumference. In other portions it is lined by silicotic masses which form the entire thickness of the cavity wall in these areas. The reason for this lies in the fact that, as the tuberculous lobular pneumonia developed in aerated tissue, it is bordered in some regions by large silicotic foci and there is no room for either the zone of granulation tissue or perifocal inflammation to develop. In other regions there is only sufficient space for an area of granulation tissue; in still others, all three layers may occur. Because of this lack of space for its development, the outer wall of fibrous tissue of the cavity is never as well developed nor has it the uniform appearance in silico-tuberculosis as in nonsilicotic pulmonary tuberculosis.

Trabeculae, almost universally present in cavities of chronic pulmonary tuberculosis, are often absent in silico-tuberculosis, especially in the cases with

marked fibrosis. The absence of trabeculae can be accounted for by the fact that the pulmonary arteries are obliterated and incorporated into the silicotic nodules, due to the destruction of the elastic fibres of the arterial walls by the productive silicotic process. As the caseation and liquefaction from the surrounding zones encroach upon the foci there are no arteries remaining with which to form trabeculae. In chronic pulmonary tuberculosis and in silico-tuberculosis, where the silicotic foci are small, there is no such destruction of the larger vessels. It is the productive reaction and not the caseation which destroys the elastic fibres. Therefore the blood vessels running through the zone of caseous lobular pneumonia show a marked narrowing of their lumina by intimal thickening, but the elastic layers of the wall are intact when examined with the elastica-van Gieson stain. When liquefaction occurs, the obliterated blood vessels remain as trabeculae which traverse the cavity.

It is interesting that there were 6 patients (11.3 per cent) who died of a fatal haemorrhage resulting from the rupture of an aneurysm of the pulmonary artery within the cavity. This compares with an incidence of 4 per cent which we previously observed in our general autopsy material. The explanation for this may again be attributed to the destruction of elastic fibres by the silicotic foci. If there has not been complete obliteration and incorporation of the vessel into the nodule, a weakened patent artery will remain to form part of the cavity wall The uncomplicated case of chronic pulmonary tuberculosis has only the productive element of the tuberculous process with which to develop an aneurysm. The case of silico-tuberculosis has not only this productive reaction, but the productive reaction of the silicotic nodule as well.

Lymph node: The tracheobronchial and peribronchial lymph nodes showed no gross evidence of caseation in any of the 54 cases. The nodes were enlarged, often markedly, and were slate gray or slate gray-black in color. They cut with great resistance.

Microscopical appearance of the lymph nodes revealed the presence of tuberculosis in all of the 53 cases showing chronic pulmonary tuberculosis. The tuberculous changes in the lymph nodes were much less extensive than in the lung, since the involvement of the node depends chiefly upon the lymphatic drainage of tubercle bacilli from the tuberculous foci. Since the silicotic process produces extensive blocking of the intrapulmonary lymphatic system, it is obvious why few bacilli reach the lymph nodes. The lymph nodes usually contain small areas of caseation, mainly in regions previously uninvolved by the silicotic process, the areas of caseation being surrounded by epithelioid cells, giant cells and fibroblasts. Frequently the caseation extends to involve the neighboring silicotic areas. Small epithelioid giant cell tubercles are frequently seen in the node. The greater part of the node, however, is composed of intact silicotic nodules.

CLINICAL ASPECTS

The exact onset of tuberculosis was usually very difficult to determine from the history alone. Productive cough, dyspnoea, weight loss and chest pain were, each or all, frequently present for many years and one could only infer

that, when these symptoms became more severe or incapacitating, the tubercle bacillus had gained a foothold. It was only in the 3 cases that will be discussed below that the onset of the tuberculous involvement could be determined more or less exactly, since the patients were under observation during the transitional period.

We feel that the diagnosis of tuberculosis in the silicotic patient rests entirely with the laboratory and its ability or failure to demonstrate tubercle bacilli in the sputum, gastric contents, pleural fluid, urine, pus from abscess or whatever other material is available for study. Similar observations were made by Ornstein and Ulmar (10) and Taylor and Alexander (11). A clue may be obtained from the chest roentgenogram by the demonstration of definite excavations, as well as from the temperature chart. The 3 cases mentioned above were all afebrile until the onset of their tuberculosis. Neither of these clues, however, are of any assistance in differentiating tuberculosis from other pulmonary infections. In 6 of the cases of silicosis who revealed no evidence of tuberculosis at autopsy, but who had other types of pulmonary disease, the roentgenograms and clinical symptoms alone were of no assistance in establishing a diagnosis.

All our cases revealed tubercle bacilli in the sputum with the exception of one patient who died so soon after admission that his sputum could not be adequately examined.

There were 3 patients whom we had the opportunity of observing during the transition from uncomplicated silicosis to silico-tuberculosis.

Case 1, a rock driller, was admitted on the first occasion with far advanced, third-stage silicosis and complained of slight dyspnoea, productive cough and weight loss. He was afebrile. He remained for three years during which time exhaustive studies were made to determine whether or not the tubercle bacillus was an aetiological factor in his pulmonary infiltration. Forty-three sputa and gastric examinations, including guinea pig inoculations, and histological study of a cervical lymph node failed to reveal evidence of tuberculosis. He was discharged and for five years continued in fair health, except for increasing cough and dyspnoea. During this time he was followed in the out-patient department where frequent sputa and roentgenographic examinations were made. One month before readmission his cough became more productive and tubercle bacilli were demonstrated in the sputum, without difficulty, on simple smear examination. At this time, he also "streaked" blood occasionally, developed severe chest pains and had a low-grade temperature. It is interesting that his chest roentgenogram on readmission differed from that taken on discharge, less in the extent of the infiltration than in the presence of highlights strongly suspicious of excavation. He expired two years after readmission with progressive pulmonary insufficiency and bilateral cavernous disease.

Case 2, a hard coal miner, presented a similar picture, except that the silicosis on the first admission was less extensive than in case 1. He was observed for two and one-half years during which time he was afebrile and tubercle bacilli were never demonstrated in the sputum or urine. He was readmitted four years later when tubercle bacilli were discovered in his expectoration. His symptoms were essentially the same as on his first admission, except for increasing dyspnoea. The chest roentgenogram showed extension of the silicosis, as well as highlights suspicious of excavation. He expired two

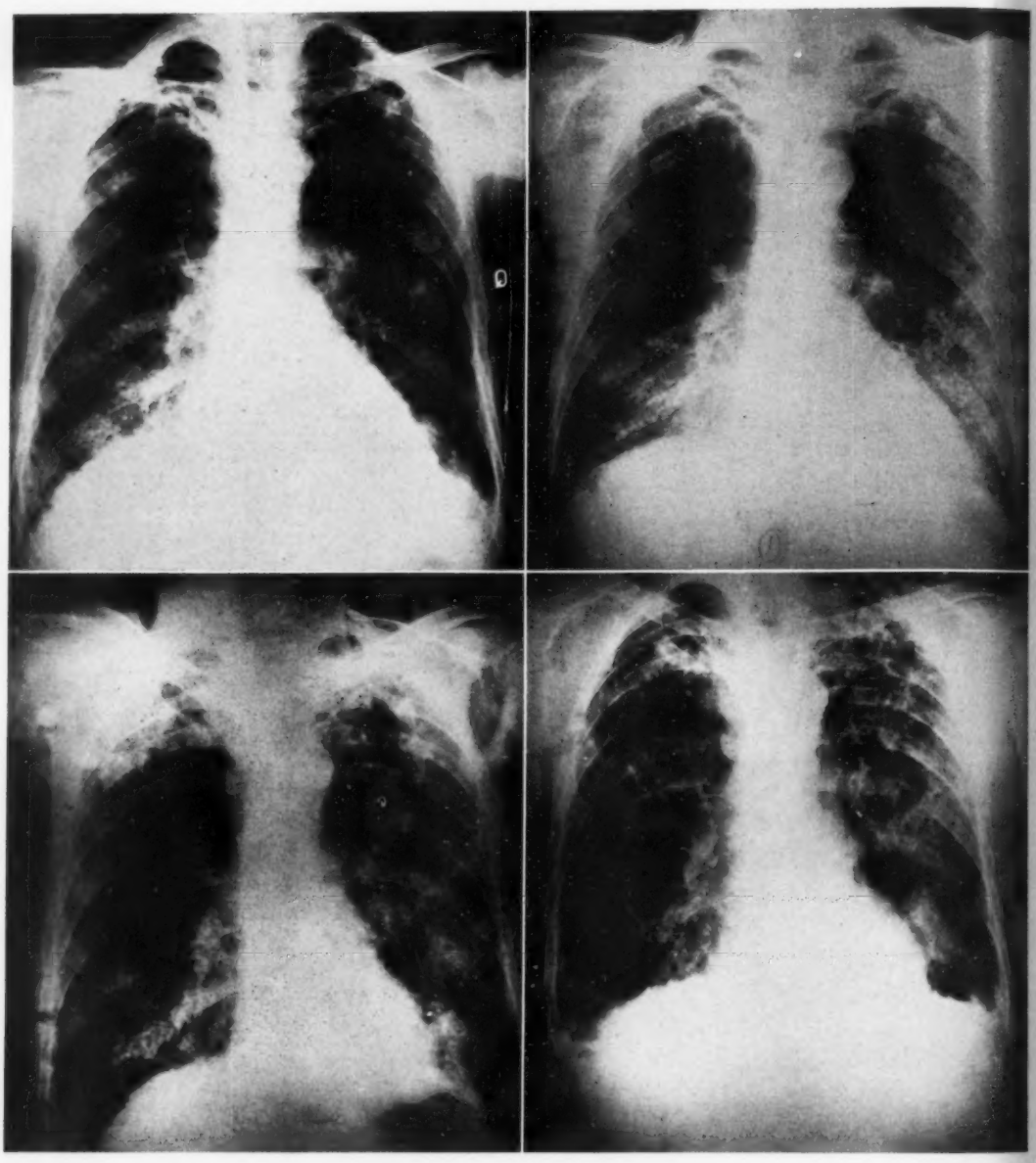

FIG. 1. Case 2. (Upper left) A—1936. First admission of hard coal miner. Increase in density of lung markings with "beads" along the thickened markings. Diffuse bilateral nodular infiltration, chiefly in lower lobes. No evidence of excavation.

(Upper right) B—1938. Patient working as hospital messenger. There has been progression of the silicotic process.

(Lower left) C—1940. Second admission. Sputum now positive. Highlights in left lung.

(Lower right) D—1942. Few months before death. Giant excavation in left mid-lung field. Smaller cavities throughout the upper lobe. Autopsy confirmed these findings. Highlights suggestive of cavitation in the right upper lobe were found to be emphysematous blebs.

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years after readmission. Postmortem examination revealed less extensive tuberculosis, but more extensive silicosis than in case 1.

Case 3, a rock driller, was under our observation for seven years. Until the last three months of life, tubercle bacilli were never demonstrated and he was kept in a tuberculosis hospital only because his severe dyspnoea warranted hospitalization and there was no other available institution to which he could be sent. He was afebrile and there was no essential change in his status during this period, except for slight progression of his marked silicosis on serial roentgenographic examinations. A few months before death he became febrile, tubercle bacilli were easily demonstrated in the sputum and at approximately the same time a chest roentgenogram revealed a sloughing out of the left upper lobe. Postmortem examination revealed extensive silicosis of the lung, minimal tuberculosis without excavation on the right and extensive cavitation of both upper and lower lobes on the left.

It is interesting that these 3 cases lived on open wards surrounded by patients with positive sputa for three years, two and one-half years and seven years, respectively, without developing pulmonary tuberculosis. These 3 patients, at least, apparently had no great predisposition to tuberculosis. Similarly, those 9 silicotic patients in whom no pulmonary tuberculosis was found at autopsy, but who lived on the open wards under similar conditions for several months, were also apparently not predisposed by their silicosis to tuberculosis.

THERAPY

In 8 of the 53 cases an artificial pneumothorax was attempted. All 8 were ineffective either because it was impossible to induce it because of an adhesive pleuritis, or it was abandoned during life because it was considered unsuccessful, or it was considered ineffective by autopsy standards.

Four patients underwent thoracoplasty operations. Two of these died from shock and paradoxical respiration immediately following the first stage. The other 2 died following three stages and revision; patent cavities were found in the lungs in all cases.

We do not hold out much hope for success with collapse therapy in silico-tuberculosis. This is particularly true in those cases with the more extensive silicosis, since the wide zones of fibrous tissue (silicotic areas) form a resistant barrier to collapse of lung tissue. This is in contrast to the fibrosis of uncomplicated pulmonary tuberculosis where the lung is more easily compressible, the site of the greatest collapse being in the more involved areas, if there are no interfering adhesions. The reason for this is the basic difference in the formation of fibrosis in tuberculosis and silicosis. In tuberculosis there is a destruction of the elastic elements of the lung and a replacement of these portions by connective tissue. As a result of this, there is a decrease in the volume of the pulmonary parenchyma in these fibrotic regions and the lungs outside the body, as well as in, collapse more easily than the healthy portions. The fibrosis in silicosis occurs chiefly along the course of the lymphatic vessels, in the interlobular septa. The silica particles in this region stimulate the formation of new collagen fibrils

to form connective tissue, but since there are no elastic fibres in the septa, there are none to be destroyed. The destruction of elastic tissue per unit of fibrous reaction is therefore far less than in the tuberculous productive process. The lungs of the silicotic are heavier, more voluminous, and have no tendency to collapse outside of the body, much less inside it. Rational collapse therapy must therefore consider not only the extent of cavitation, but also the extent of silicosis.

CAUSES OF DEATH

From table 5 it may be seen that pulmonary tuberculosis was the cause of death in 41 (76 per cent) of the cases. Death in these patients was caused by the pulmonary insufficiency resulting from the development of tuberculosis in whatever functioning lung parenchyma had escaped the silicotic nodules. If the silicosis is marked, the tuberculous process need not be extensive to result in insufficiency.

Death was due to cardiac failure in 4 cases. This is compatible with the age incidence of this series, as well as being the usual cause of death in uncomplicated silicosis. In comparing the size of the heart in the silico-tuberculosis group with

TABLE 5

Causes of death

PROGRESSIVE PULMONARY TUBERCULOSIS	CARDIAC	TUBERCULOUS MENINGITIS	POSTOPERATIVE	TOXAEMIA	URAEMIA
41 (76%)	4 (7.5%)	2 (3.5%)	3 (6.0%)	2 (3.5%)	2 (3.5%)

that of the group with pulmonary tuberculosis without silicosis, we found the former to be generally larger. Thirty-three per cent of the silicotic hearts and 24 per cent of the nonsilicotic weighed 360 g. or over. Thirteen per cent of the silicotic and 26 per cent of the nonsilicotic weighed under 250 g.

One of the 2 patients who died of tuberculous meningitis had a generalized miliary tuberculosis. This is in contrast to Strachan (5) who found tuberculous meningitis a not infrequent fatal termination. Two of the 3 surgical deaths followed a first-stage thoracoplasty and one, a gastric resection of the stomach for carcinoma. Of the 2 cases of uraemia, one was due to amyloid nephrosis.

CONCLUSIONS

In order to determine whether or not pneumonoconiosis alters or is itself altered by pulmonary tuberculosis, we have reviewed 54 cases of silico-tuberculosis and compared them with 9 cases of pneumonoconiosis without tuberculosis and 200 cases of tuberculosis without pneumonoconiosis. We have found that, although silicosis and tuberculosis exist concomitantly in the same lung, each maintains its individual integrity. The tuberculosis apparently alters the silicosis not at all. The pneumonoconiosis alters the tuberculosis only in so far

as the silicotic nodules prevent the full development of tuberculous granulation tissue and, in the walls of cavities, the pyogenic membrane. Both granulation tissue and pyogenic membrane, however, are present in those portions of the lung where the silicotic foci are small or absent.

Except for this quantitative difference we have found very little variation in the tuberculous process, whether or not pneumonoconiosis is present. The size, situation and number of cavities are approximately the same. There is a slightly greater incidence of perforation of cavities through the interlobar fissures in the silicotics and a greater incidence of death from fatal pulmonary haemorrhage. The latter factor is due to the greater productive reaction in the silicotic lung with greater opportunity to develop an aneurysm of a branch of the pulmonary artery.

We have found it difficult to determine the exact time at which pulmonary tuberculosis was superimposed upon pneumonoconiosis, unless the patient was under observation during the transition period, since the symptoms of the two diseases are so similar. While fever and definite evidence of cavitation on roentgenography are useful diagnostic aids, the final conclusion must be based upon the demonstration of the tubercle bacillus.

We have found collapse therapy to be of little value in cases of silicotuberculosis. This is apparently due to the fact that the silicotic lung remains voluminous and shows no tendency to collapse. The pathological reasons for this have been discussed.

Most cases succumbed to progressive pulmonary insufficiency. When the tuberculous process invaded the remaining portions of resilient lung tissue sufficiently, death was inevitable.

CONCLUSIONES

A fin de determinar si la neumonoconiosis altera o es alterada por la tuberculosis pulmonar, se repasaron 54 casos de silicotuberculosis, comparándolos con 9 casos de neumonoconiosis sin tuberculosis y 200 casos de tuberculosis sin neumonoconiosis, habiéndose descubierto que aunque ambos estados coexisten en el mismo pulmón, cada uno retiene su integridad propia, sin que la tuberculosis aparentemente modifique en lo más mínimo la silicosis. La neumonoconiosis sólo modifica la tuberculosis en el sentido de que los nódulos silicóticos impiden el pleno desarrollo de tejido tuberculoso de granulación y en las paredes de las cavernas, de la membrana piógena, pero encuéntranse presentes tanto dicho tejido como la membrana en las porciones del pulmón en que los focos silicóticos o son pequeños o no existen.

Salvo por esa diferencia cuantitativa, nótase muy poca variación en el proceso tuberculoso, haya o no neumonoconiosis presente. El tamaño, situación y número de cavernas vienen a ser idénticos, aunque en los silicóticos existe un índice ligeramente mayor de perforación de cavernas a través de las grietas interlobulares y una mortalidad mayor producida por hemorragias pulmonares. Este último factor procede de la mayor reacción exudativa en el pulmón silicótico y de haber más ocasiones de que se forme un aneurisma en una rama de la arteria pulmonar.

Por ser tan semejantes los síntomas en ambos males resulta difícil determinar el momento exacto en que la tuberculosis pulmonar se sobrepone a la neumonoconiosis, salvo cuando el enfermo ha estado en observación durante el período de transición. Aunque la fiebre y los signos roentgenográficos precisos de cavernas resultan auxiliares útiles en el diagnóstico, la conclusión definitiva tiene que basarse en el hallazgo del bacilo tuberculoso. La colapsoterapia resulta de poco valor en los casos de silicotuberculosis, lo cual se debe aparentemente a que el pulmón silicótico retiene su volumen y no muestra tendencia al colapso, habiéndose discutido las causas patológicas de este fenómeno.

La mayor parte de los enfermos sucumbieron de una insuficiencia pulmonar cada vez más avanzada. Una vez invadidas por el proceso tuberculoso las porciones restantes del tejido pulmonar elástico, la muerte resultó inevitable.

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THE QUANTITY OF FOCAL (TUBERCLE) CALCIUM IN HUMAN LUNGS[1,2]

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During the course of chemical studies on a series of human lungs, data were obtained on the quantity of calcium salts found in the form of calcified foci. Most of this focal calcium is presumably derived from old tubercles in the lung parenchyma and in the intrapulmonic peribronchial lymph nodes. Numerous surveys have been made at necropsy (1, 2, 3, 4) and with roentgenograms during life (5, 6) on the incidence, number, size, location, configuration and density of such calcium deposits. The present study presents quantitative data on this focal calcium, and attempts to correlate it in respect to number, size, incidence and density of the lesions with the roentgenograms made during life, and with age, sex, major disease and place of residence of the patients.

Calcified tuberculous foci in the lungs are of interest to epidemiologists (7, 8, 9), to roentgenologists (5, 6, 10) and to other students of tuberculosis (4, 11, 12, 13). At the present time they are also of interest to the Armed Forces, where their number and size is used as the basis for acceptance or rejection (14).

METHODS

Lungs were obtained at necropsy in a series of cases, which were unselected except to exclude those with active pulmonary tuberculosis (only one case was so rejected), at the University of Chicago Clinics and the Illinois Central Hospital of Chicago, during the years 1940 to 1943. Both are general hospitals whose patients come from Chicago and surrounding territory. The great majority are full- or part-pay. All were white. After a routine examination including microscopical sections, the lungs were separated from the mediastinal structures at the hilum and preserved in alcohol, the volume of which in cubic centimeters was equal to their weight in grams. The lobes were subdivided with a knife to facilitate preservation. To the lungs and alcohol in which they were preserved was added a 10 per cent aqueous potassium hydroxide solution equal in volume to that of the alcohol. The saponification was carried out by heating for twenty-four hours on the steam bath. The concretions, which fell to the bottom of the flask, were freed from the saponification mixture by decantation and washed several times with water by the same method. They were transferred onto a filter paper in a funnel, washed with water, air dried and weighed.

The roentgenograms made routinely during life were next reëxamined, special attention being directed to the number, size, form, and in some cases to the location of all densities suggesting calcification. Immediately after these data were recorded the bottle containing the concretions was produced and a correlation of the findings from the two sources was attempted.

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[2] This work was aided by a grant from the Commonwealth Fund.

Forty-six pairs of lungs of stillborn infants were also saponified by the same method, as one form of control. Additional controls consisted of large amounts of pooled human kidney and of heart.

RESULTS

Incidence and quantity of focal calcium: Examination for calcified foci was made on 119 pairs of lungs, of which 46 were from newborn infants.[3] The latter contained no concretions, as was to be expected. The lungs of a child of six years were also negative.

TABLE 1

Amount of focal calcium in 72 pairs of adult human lungs

AMOUNT OF FOCAL CALCIUM	NUMBER OF CASES
mg.	
None	8
0–9	4
10–19	9
20–29	5
30–49	8
50–99	8
100–199	11
200–299	5
300–399	4
400–499	4
500–599	3
Over 1,000	3

TABLE 2

Incidence and quantity of focal calcium in human lungs at various ages

AGE	NUMBER OF CASES	NUMBER WITHOUT CALCIFICATIONS	AVERAGE FOCAL CALCIUM
years			*grams*
Stillborn	46	46	0.0
0–9	1	1	0.0
10–19	1	0	0.014
20–29	8	3	0.011
30–39	11	3	0.083
40–49	6	0	0.064
50–59	21	0	0.442
60–69	16	2	0.253
70–79	8	0	0.216
80–89	1	0	0.412

The remaining 72 pairs were from adults. Eight contained no foci of calcification, while 64 (88.8 per cent) had one or more calcific bodies, together weighing from 0.004 to 4.058 g. The average yield obtained for the 72 cases was 0.231 g. Three cases each had over one gram: they yielded 4.058, 2.140 and 1.587 g. The

[3] We are indebted to Dr. Edith Potter for these infant lungs.

2.140 g. was all found in one lung, the contralateral lung having none (see tables 1 and 2).

In 11 cases the two lungs were analyzed separately, with the following result: in 2 cases neither lung contained calcified foci, in 4 cases one lung of the pair was negative while the other had focal calcium, and in 5 cases each lung yielded focal calcium.

Relation to age: As already stated the lungs of 46 stillborn infants had no focal calcium deposits. Up to the age of thirty years the average amount remained small, many lungs having none. There was a sharp rise thereafter, the peak being reached in the sixth decade when the average amount for 21 cases was 0.442 g. This figure is buoyed by the presence in this decade of the 3 cases which had over one gram each. The figures show a decrease after sixty years of age but this probably is not significant because of the small number of cases and because of the possible padding of the figure for the sixth decade. Certainly the figures show no increase beyond this age such as would be expected if the focal calcium were due to arteriosclerosis. The cases with no focal calcium were nearly all found in the younger age groups. Thus, of 21 persons under forty years of age 7 (33.3 per cent) had no tubercle calcium, and of 52 over that age only 2 (3.9 per cent) showed no concretions. These data are presented in table 2.

Relation to major disease: These persons died from the wide variety of disease encountered in general hospitals. There were not enough cases in any disease group to warrant an attempt at correlation. Seven had primary carcinoma of the lung. Their lungs had an average of 0.427 g. of focal calcium, which is the average amount for their age group. In 3 of these 7 cases the lungs, cancer and non-cancer, were analyzed separately and in every instance the former had focal calcium while the latter had none. The lungs of one patient, a man of fifty-six years who died of bilateral pulmonary tuberculosis and is not included in this report, contained 0.637 g. of focal calcium which was in the form of numerous small concretions.

In 2 cases it is believed that part, but not all, of the focal calcium was obtained from arteriosclerotic lesions, both on the basis of the roentgenograms and on the morphology of the concretions recovered chemically. In 2 additional cases it is possible that some of the calcified foci were broncholiths—at least the roentgenograms were so interpreted.

There was anatomical evidence both on gross and microscopical examination of the lungs that the 3 persons who had over one gram of focal calcium had tuberculosis of the adult type which had become inactive, in addition to a primary infection. Some lungs with less than one gram of focal calcium also showed lesions on gross examination of the type which are commonly regarded as representing the adult reinfection type of healed tuberculosis.

Relation to sex: The 41 males had an average of 0.287 g. of focal calcium and the females had 0.157 g. The average for the males was increased by the presence in this group of the 3 cases having the exceptionally large amounts of focal calcium (4.058, 2.140 and 1.587 g.). The average for the males if these 3 cases are excluded is 0.108 g., a figure lower than for the females. The 8 cases which

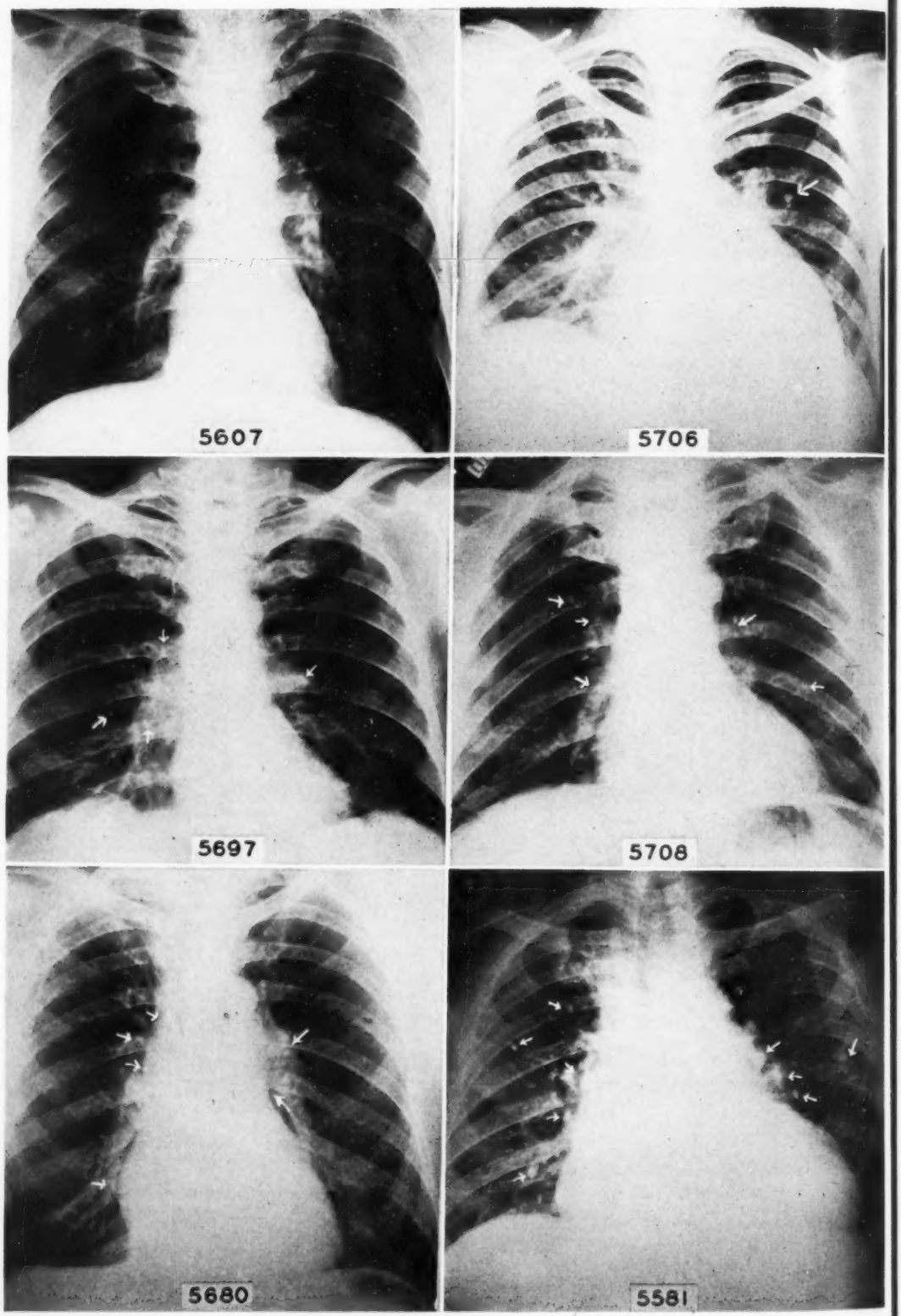

PLATE I

Roentgenograms of 6 cases. Compare with plate II. (Figure 5581 by courtesy of Dr. Wm. Culpepper.)

had no focal calcium were about evenly divided between the sexes: 5 were males and 4 were females.

Relation to place of residence: It is impossible to divide accurately these cases into rural and urban groups because of the shifting nature of the residence of many persons. Only 12 had lived their entire life in Chicago. They had an average focal calcium of 0.423 g. Forty-two gave their residence as Chicago, 17 were from Illinois outside of Chicago and 13 were residents of other states. Twenty-one were foreign born. No abnormally low or high focal calcium figures were found for any of these groups. They probably represent the population of the state as a whole more accurately than they do the city of Chicago.

The 8 cases who had no focal calcium were found to be divided between rural and urban dwellers. Three had been living in Chicago for periods from five to forty-six years, while 2 others lived in the suburbs and one lived in another city. Only 2 were rural, but one of these had been born in Chicago.

Number, size and form of the calcified foci: It is impossible to present accurate data on the form, number and size of calcified lesions following this method of chemical preparation because many foci undergo fragmentation as their capsule and support are digested away. While some of the concretions, in nearly every case, retain their form others undergo fracture so that much gravel is obtained. As already stated 8 cases had no concretions. One case had a solitary focus about 2.5 mm. in diameter, which weighed 0.0114 g. (see plate II for illustrations). One case had 5 and another had 6 small concretions; all others had more than 10. In these cases the great number was usually due to the presence of numerous irregular, sharp fragments, some of which were presumably the result of breakage.

The obviously preformed concretions were usually round or oval. Their surface was usually regular and sometimes smooth. Occasionally they appeared porous, as if ossified. They were less commonly irregular in form, sometimes having short, stubby branches. The gravel showed sharp, fractured margins. The impression was gained that the smooth, unbroken concretions were predominantly from parenchymal lesions and that the irregular and the broken pieces came largely from the lymph nodes. The same impression had previously been obtained from histological studies of tubercles in these locations and from roentgenographic studies.

Also because of the fragmentation of some of the lesions it is impossible to give complete data on sizes. Those concretions which were unbroken varied from less than one millimeter to one which measured 16 × 11 × 8 mm. in maximum dimensions and which weighed 0.619 g. Frequently several unbroken foci each up to 10 mm. were found in a single case.

The heaviest calcification weighed 0.668 g. It was not the largest, measuring only 16 × 7.5 × 7.5 mm. There appeared to be great variation in the density of the foci.

Correlation with roentgenograms: Roentgenograms were available for comparison in 50 cases. They were reviewed for the number, size, location and density of all lesions considered to be calcifications, and immediately thereafter a correlation was made with the calcified specimens which had been isolated from that lung.

In 39 cases the roentgenological and chemical studies were in agreement with respect to the presence or absence of focal calcium; in 36 cases both were positive, and in 3 cases both methods were negative (see table 3).

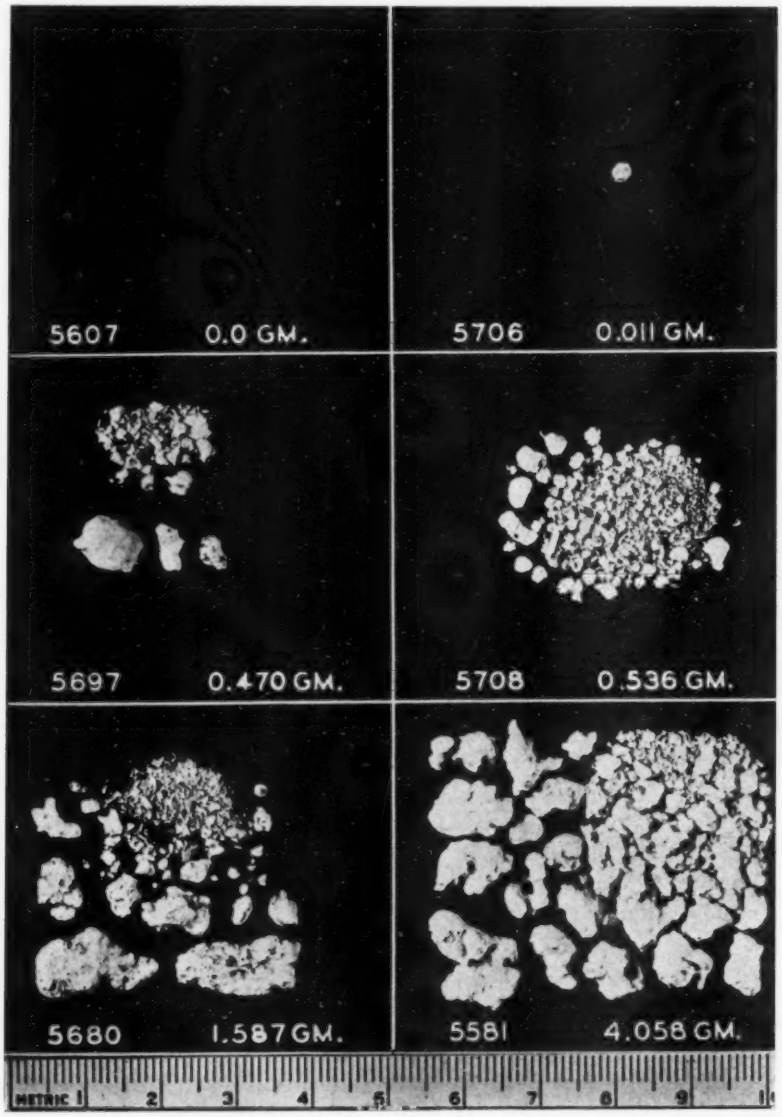

PLATE II

Photograph of the focal calcium obtained from the same cases illustrated in plate I, showing the size, number, configuration and quantity of calcium.

The smallest amount of focal calcium which was seen on the roentgenograms was 9 mg. Additional cases containing small amounts which were seen had 11, 14, 14, 16, 16, 18, 21 and 24 mg. They demonstrate that minute amounts of focal calcium may be seen under favorable conditions.

Among the cases in which the roentgenograms showed focal calcium were 20 in which the concretions recovered chemically were under 100 mg. These cases were reviewed to determine why such small amounts were visible. In all of them at least part of the focal calcium was located in a peripheral portion of the lung.

In 11 cases the chemical studies yielded focal calcium while the roentgenograms revealed none. The films in these cases were then reëxamined in an attempt to explain the discrepancy. In 4 of them intrathoracic lesions were present which accounted for the failure to recognize the calcified foci. These lesions were hydrothorax in 2 cases, advanced pulmonary congestion in one case and metastatic carcinoma in one case.

The amount of focal calcium recovered in the remaining 7 cases was 125, 49, 16, 16, 5, 4 and 4 mg. respectively. In 5 of these 7 cases the roentgenograms showed small densities which had been interpreted as blood vessels, although, in retrospect, they might have been calcium foci.

TABLE 3

Amount of focal calcium in 36 cases in which the roentgenograms were positive

AMOUNT OF FOCAL CALCIUM	NUMBER OF CASES
mg.	
Under 10	1
10–19	6
20–29	3
30–49	4
50–99	6
100–199	6
200–299	3
300–399	3
Over 400	4

It was difficult to understand how the foci containing 125 and 49 mg. were overlooked in the roentgenograms. The possibility that the concretions which were recovered were not calcium occurred as an explanation. Consequently they were subjected to chemical analysis which showed that they contained calcium, the results resembling those of Maver and Wells (15) very closely. In these 2 cases then, the failure of roentgenographic demonstration of fairly large amounts of calcium must be attributed to unfavorable location.

DISCUSSION

Focal calcium-containing deposits in the lungs may be either ossifications or calcifications. The former occur in bronchial cartilages, old tubercles (12), osteogenic sarcoma metastases, ossifications of idiopathic type (16) and other lesions. Calcification most commonly occurs in tubercles but may be found in many other lesions such as coccidioidal granuloma (17), pulmonary arteriosclerosis (18), lung and bronchus stones, bronchial cartilages, metastatic calcification (19), after trauma and as idiopathic lesions (7, 9, 20, 21, 22).

In this survey it is assumed that the great majority of the concretions were formed in tubercles. This assumption is based on microscopical examination of many similar lesions made in the past in this department and in this vicinity also by Sweany (12), and on the roentgenographic evidence. While microscopical observations may not give an absolutely conclusive differentiation between calcification in tubercles and in other lesions, the information so obtained, when taken in conjunction with clinical and other data, is fairly reliable. There is reason to believe that the total number of cases of focal calcification due to causes other than tuberculosis is low in this part of the country so that, by comparison with the high percentage having calcified tubercles, the inclusion of a few nontuberculous foci among the tuberculous could hardly cause a great error. In this series of cases pulmonary arteriosclerosis may have been present in 2 cases and broncholithiasis in 2 cases, but this accounts for only part of the focal calcium in these 4 cases, and does not alter the percentage of cases considered to have tubercle calcium.

Other human tissues examined by similar chemical methods do not have comparable amounts of focal calcium. Other organs examined on a large scale have been kidney and heart. For example, from 19,464.0 g. of kidney tissue 0.256 g. of particulate calcium salts was recovered, while from 24,264.0 g. of heart the amount was 4.156 g. In both instances the calcium deposits were not found in the form of preformed, smooth, round concretions but in flat or curved, flaky placques. They resembled the calcified arteriosclerotic lesions so commonly seen in the arteries of these two organs, especially the latter. They are presumably arteriosclerotic and not tubercle focal calcium.

No data have been found in the literature on the quantity of focal calcium found in a series of human lungs which might be used for comparison with the present series. An analysis of the qualitative composition of such foci was made by Maver and Wells (15), who found little silica, and a chemical composition similar to that of other calcified pathological tissues and also normal bone.

In the past, three methods have been available for making surveys on the incidence of tuberculous infection in a population. They are tuberculin surveys, mass roentgenographic examinations and postmortem anatomical studies. To these is now added a fourth method, namely, that of postmortem chemical studies for focal calcium. Each of these methods has advantages as well as disadvantages. The latter two methods share the disadvantage of being exclusively postmortem surveys. This, however, gives them a certain objectivity not shared by the other methods. The chemical method reported here has the advantages of simplicity, ease, and low cost in time and materials as compared with the anatomical section method. It has the disadvantage of failure to distinguish between tuberculous and nontuberculous calcifications, a defect which it shares with roentgenographic surveys and, in part at least, with the anatomical section method. This should not lead to serious error in regions where nontuberculous calcifications are few. This method also has the disadvantage of failure to detect noncalcified tuberculous lesions, some of which might be found on careful anatomical study. On the other hand lungs which have been subjected to careful anatomical disection might still contain concretions demonstrable by this chemi-

cal method. The frequency of such an occurrence should be easy to determine by subjecting a few lungs, on which the anatomical study has been finished, to saponification.

Since no postmortem surveys on the incidence of tuberculous infection have previously been made in this region, there is no basis for comparison of the reliability of the incidence of infection reported here. The figure found (88.8 per cent), however, corresponds closely to that reported recently by Carnes (4) for Baltimore (90 per cent). A comparison of the chemical and the roentgenographic methods, undertaken in 50 of the cases reported here, shows that the former was considerably more delicate. Roentgenologists concede that small calcifications in some parts of the lungs can be overlooked unless unusual techniques are used.

In the present survey the tracheal and peribronchial lymph nodes in the mediastinum were excluded. They have generally been included in the anatomical studies made in the past. In future studies they should be included because they may show tuberculous lesions in cases where none were demonstrable in the lungs. This would raise the percentage of infected persons discovered in the population under survey.

SUMMARY

A simple method is presented for the quantitative determination of focal calcification in the lungs and other tissues, together with the results of its use in 119 pairs of human lungs. Focal calcium was found in 88.8 per cent of 72 pairs of adult lungs. The average amount was 0.231 g. The quantity and the incidence of positive cases increased sharply between the thirtieth and fifty-ninth years, but not thereafter. No important differences were detected in the quantity found in the two sexes or in rural and urban dwellers. The heaviest concretion weighed 0.668 g. and the largest measured 16 × 11 × 8 mm. They were usually multiple. On the basis of previous morphological studies, roentgenograms, tuberculin surveys and by exclusion it is believed that the great majority of these foci are calcified tubercles, and that this method can be used to make postmortem surveys on the incidence of tuberculous infection.

A comparison of the reliability of this chemical method with roentgenograms in detecting calcified foci was made in a series of 50 cases. In 39 cases (78 per cent) there was agreement, while in 11 (22 per cent) calcified foci were recovered chemically which the roentgenograms did not reveal. The causes of failure were chiefly concomitant disease in the chest and small amount of focal calcium located not in the lung fields. The amazing sensitivity of roentgenograms for detecting small calcified foci located in the lung fields was shown by the demonstration of a lesion containing as little as 9 mg., and others of small amounts. In this series the chemical isolation was more reliable than the roentgenograms in detecting calcified lesions and, presumably, the incidence of tuberculous infection.

SUMARIO

Preséntase un método sencillo para la determinación cuantitativa de la calcificación focal en los pulmones y otros tejidos, junto con el resultado del empleo de esta técnica en 119 pares de pulmones humanos. Descubriéronse focos o

depósitos de calcio en 88.8 por ciento de 72 pares de pulmones adultos, promediando 0.231 gm. La cantidad y la frecuencia de casos positivos aumentó decididamente entre los treinta y los cincuenta y nueve años, pero no después. No se descubrieron importantes diferencias en las cantidades descubiertas en los dos sexos, ni en los residentes de los campos o las ciudades. La concreción más pesada representaba 0.668 gm. y la mayor medía 16 por 11 por 8 mm. Los depósitos fueron por lo general múltiples. Tomando por base previos estudios morfológicos, roentgenogramas, encuestas por tuberculina y por exclusión, piénsase que la mayoría de esos focos representaba tubérculos calcificados y que puede emplearse la técnica para realizar encuestas autópsicas acerca de la frecuencia de la infección tuberculosa.

En una serie de 50 casos compárase la exactitud de este método químico con los roentgenogramas en los descubrimientos de focos calcificados. En 39 (78 por ciento) hubo acuerdo, mientras que en 11 (22 por ciento) se descubrieron químicamente focos calcificados que no revelaron las radiografías. Las causas de este fracaso fueron principalmente afección concomitante en el tórax y pequeños focos de calcio que no estaban situados en los campos pulmonares. La asombrosa sensibilidad de los roentgenogramas para descubrir pequeños focos calcificados situados en los campos pulmonares quedó demostrada por el hallazgo de una lesión que no contenía más de 9 mg., y otros también pequeños. En esta serie el aislamiento químico resultó más fidedigno que los roentgenogramas para descubrir lesiones calcificadas y, presuntamente, la incidencia de infección tuberculosa.

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TUBERCULOUS STENOSIS OF MAJOR BRONCHI[1]

Its Diagnosis by Rhonchi, Verified by Bronchoscopy

MACK McCONKEY AND JOSEPH GORDON

The classical description and appraisal by Laennec (1) of rhonchi in the diagnosis of bronchial stenosis has not been surpassed. Referring to the dry sonorous rhonchus, Laennec states: "I apprehend it can hardly exist in bronchial tubes of a small diameter." And, "It would seem to depend rather on some alteration in the shape of the tubes through which the air passes, and I am disposed to attribute it in most cases to the contraction from some cause or other, of the origin of the bronchial branch. This contraction may be either permanent or temporary, and may be occasioned by the pressure of an enlarged gland, or of a circumscribed spot of inflammation, the presence of a tenacious clot of mucus, or the local thickening of the mucus membrane." In addition to his description, two further observations by one of us have been helpful in the detection of a tuberculous lesion producing stenosis of a major bronchus (2). They are: the elicitation of rhonchi by the aid of posture, and the more marked intensity of this sign over the area of the affected bronchus. Moreover, we were able to confirm Laennec's observation that rhonchi are produced by "a circumscribed spot of inflammation" in a bronchus, thus permitting one to recognize the complication in the early stages of its development.

The present study comprises 95 adult patients with pulmonary tuberculosis and tubercle bacilli in the sputum, who presented no evidence of collapse of the lung. Of this number, 61 patients had persistent rhonchi unrelieved by cough; 22 men and 39 women. There were 8 in the incipient, 22 in the moderately advanced and 31 in the far advanced stage of the disease. The evidence of the complication was considerably higher in women than in men, confirming a previous finding by us and others (3, 4).

The observations on rhonchi which proved helpful in determining the presence and the site of the bronchial lesions are as follows: The development of persistent sonorous rhonchi unrelieved by cough during the course of pulmonary tuberculosis signifies, with rare exceptions, the presence of bronchial stenosis. It is important to remember that careful questioning of the patient may be necessary to elicit a history of this sign, described by the patient as wheezing. In distribution, the rhonchi are local or general, and in character they may be sibilant, but in most instances they are predominantly or exclusively sonorous. The sign is more marked during expiration and may be heard only at the end of forced expiration, attributed, in part at least, to the narrower calibre of the bronchus during this phase of respiration. The rhonchi are usually more readily palpable and invariably loudest over the stenotic bronchus (figure 1). This latter observation is valuable in locating the site of the affected bronchus and in differ-

[1] From the New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

entiating bronchial stenosis from such conditions as asthma and chronic bronchitis. In certain instances, rhonchi cannot be elicited except when the patient is

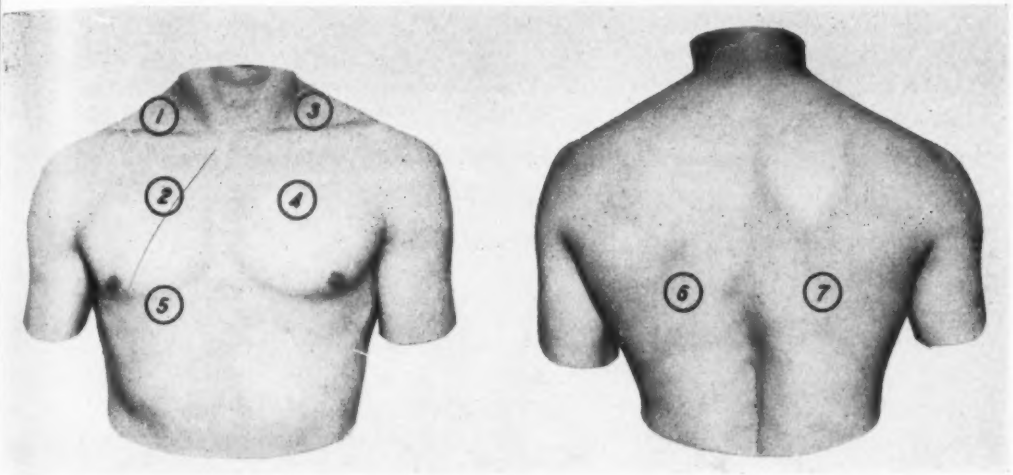

FIG. 1. The rhonchi are loudest and usually palpable at points 1 or 2 in stenosis of the right main bronchus or its branch to the upper lobe; at points 3 or 4 in stenosis of the left main bronchus or its branch to the upper lobe. In stenosis of the middle lobe bronchus, the area of intensified rhonchi is at point 5; for the left lower lobe, at point 6, and for the right lower lobe bronchus at point 7.

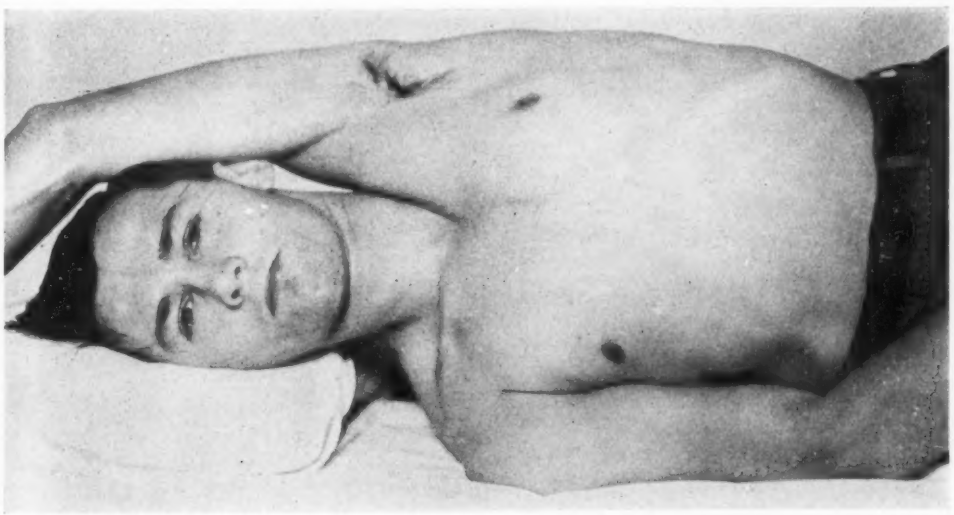

FIG. 2. Patient lying on side of affected bronchus with shoulder depressed

lying on the side of the affected bronchus, with the shoulder depressed, as illustrated in figure 2. The procedure, first described by Upham (5) and amplified by Kegel (6), for the demonstration of râles is likewise helpful for the elicitation

of rhonchi and should not be omitted if there is reason to suspect the presence of the complication.

In this series of 95 tuberculous patients, there were 61 who during the course of the disease developed persistent sonorous rhonchi unrelieved by cough. In no less than 58, or 95 per cent, the diagnosis of a stenotic lesion of a major bronchus was verified by bronchoscopy. In the remaining 3 instances, the bronchial tree was normal in appearance insofar as could be determined by bronchoscopy. In other words, the correlation between persistent sonorous rhonchi and bronchial stenosis was quite striking.

The remaining 34 patients in this series, with comparable extent of pulmonary tuberculosis, at no time presented, insofar as could be determined, persistent rhonchi unrelieved by cough, and were regarded as a control group. By bronchoscopic examination there was no evidence of disease of the major bronchi in 32. In the remaining 2 instances there was a localized inflammation of a main bronchus, and one of these presented a very small ulcer. The data in this control group of 34 patients suggest that with few exceptions stenosis of a major bronchus may be excluded in the absence of persistent sonorous rhonchi.

The site of the lesion, in most instances, can be determined by physical examination, since the rhonchi are more readily palpable and of the greatest intensity over the affected bronchus. This area of intensified rhonchi, however, is usually the same for stenosis of the main bronchus as for a lesion of the adjoining bronchus to the upper lobe, and lies just lateral to the mid-portion of the sternum, occasionally over the summit of the chest. In stenosis of the bronchus to the lower lobe, this area is over the lower part of the thorax posteriorly. In stenosis of the bronchus to the middle lobe, it is just lateral to the lower end of the sternum (figure 1).

The distribution of the stenotic lesions is presented in table 1. In this series it was possible to state correctly in every instance whether the stenotic lesion was present in a major bronchus to the right or to the left lung, as verified by bronchoscopy. It was not possible by the aid of this sign to state whether the lesion was present in the main bronchus or in the adjoining branch to the upper lobe. Stenotic lesions in the lower lobe were differentiated from similar lesions of the main bronchus or of the upper lobe bronchus in the 8 instances occurring in this series. The single instance of stenosis of the bronchus to the middle lobe was correctly located by the aid of rhonchi. The data reveal a striking correlation between the physical and the bronchoscopic examinations in locating the site of the affected bronchus. The sign, however, is not serviceable for determining the character of the endobronchial lesion.

Bronchoscopy: The retrograde lens extending the field of vision was used in the bronchoscopic examination of the 95 patients included in this series. The lesions, by their surface appearance, may be conveniently classified as follows: localized bronchitis, ulcerative, hyperplastic granulations and fibrostenotic. The incidence and the type of these lesions are presented in table 2. The most commonly encountered lesion was a localized bronchitis. In the present series it

occurred in 25, or 40 per cent. The intact mucosa presents a localized area of redness and swelling and bleeds readily from slight trauma. Unfortunately, we were not able to follow the course of these lesions in most instances. However, we have noted that spontaneous healing has occurred in a number of these cases accompanied by disappearance of rhonchi. In others, the lesions have gone on

TABLE 1

Distribution of bronchial lesions in 60 cases*

Single lesions:	
Right main bronchus	7
Right upper lobe	7
Right lower lobe	2
Right middle lobe	1
Left main bronchus	22
Left upper lobe	6
Left lower lobe	5
	50
Multiple lesions:	
Trachea and right main bronchus	4
Trachea, left main and right main bronchus	1
Trachea and left main bronchus	4
Trachea, left main and left lower bronchus	1
	10

*58 cases with physical signs of bronchial stenosis and 2 without.

In 10 instances the trachea was also involved. Lesions confined to the trachea cannot be recognized clinically except in the presence of marked stenosis.

TABLE 2

Incidence and type of bronchial lesions

STAGE OF PULMONARY DISEASE	LOCALIZED BRONCHITIS	ULCERATION	HYPERPLASTIC GRANULATION	FIBROSTENOSIS	TOTALS
Incipient	2	1	4	1	8
Moderately advanced	11	1	3	6	21
Far advanced	12	2	8	9	31
	25	4	15	16	60

to ulceration, and in still others retrogressive ulcerative lesions eventually appeared as localized areas of inflammation. According to Myerson (7), these early lesions are tuberculous in nature, and our limited observations tend to support this view. The remaining lesions, ulcerative, hyperplastic granulation, and fibrostenotic, are well recognized, as are their complications—obstructive emphysema and atelectasis—and for this reason need no further comment.

Tuberculous patients presenting the following abnormalities of the major bronchi were excluded from this study:

Collapsing bronchus: In 5 instances the mucosa of the trachea and major bronchi was normal in appearance on bronchoscopic examination. It was noted, however, that each patient presented a main bronchus, which at the end of expiration contracted to a slit-like aperture while the corresponding bronchus on the opposite side did not. The exact nature of the underlying condition producing this effect is not definitely known. It has previously been described by Eloesser (8), Myerson (7) and others. In all 5 instances the rhonchi were persistent and similar to those encountered in stenosis of a major bronchus.

There were 3 instances of persistent and localized sonorous rhonchi occurring in tuberculous patients where the stenosis was caused by extrabronchial pressure. In an additional case the persistent rhonchi were due to a nontuberculous polyp occurring in a major bronchus.

Persistent sonorous rhonchi not infrequently first appear after the induction of pneumothorax. This observation may be reasonably explained on the basis that the procedure diminishes the calibre of the affected bronchus, thereby accentuating the stenosis with the consequent production of rhonchi. The rhonchi originating in the collapsed lung are muffled and therefore a comparison of the intensity of the rhonchi on the two sides of the chest is not helpful in locating the site of the stenotic lesion. Conversely, in thoracoplasty and operations on the phrenic nerve, the sign may prove helpful.

CONCLUSIONS

The development of persistent sonorous rhonchi in the course of pulmonary tuberculosis justifies, with few exceptions, the diagnosis of stenosis of a major bronchus. The complication is usually tuberculous in nature. On physical examination the rhonchi are usually more readily palpable and invariably loudest over the affected bronchus, an observation helpful in locating the site of the stenotic lesion. At times the sign cannot be elicited without the patient being in the recumbent position. This posture is helpful in recognizing early tuberculous lesions of the bronchi. However, a bronchoscopic examination is necessary to determine the surface appearance and extent of the lesion as well as the degree of bronchial stenosis.

CONCLUSIONES

La aparición de estertores sonoros persistentes en el curso de la tuberculosis pulmonar justifica, con pocas excepciones, el diagnóstico de estrechez de un bronquio mayor. La complicación suele ser de naturaleza tuberculosa. Conforme al examen físico los estertores suelen ser más palpables y generalmente más fuertes sobre el bronquio afectado, cuya observación resulta útil para localizar el asiento de la lesión estenótica, aunque a veces no puede evocarse este signo a menos que se haga recostar al enfermo, posición ésta que resulta útil para reconocer las lesiones tuberculosas tempranas de los bronquios. Sin embargo,

se necesita el examen broncoscópico a fin de determinar el aspecto superficial y extensión de la lesión, así como la intensidad de la estrechez bronquial.

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SARCOIDOSIS[1]

One Case Report and Literature Review of Autopsied Cases

ELI H. RUBIN AND MAX PINNER

The interest in sarcoidosis has obviously quickened during the last few years. There is no reason to assume that its frequency is increasing, but rather that more physicians have become aware of its existence. After one of us (M. P.) had published a literature review of sarcoidosis in 1938 (26), several dozens of histological slides and roentgenograms were received from many parts of the country, all concerned with the differential diagnosis of sarcoidosis—and the majority of these cases had been properly diagnosed as sarcoidosis. This personal experience and the ever increasing numbers of case reports during the last few years are indicative of the growing interest centered around this disease.

In the literature review, referred to above, a total of 18 postmortem reports were listed. In the meantime, 25 more reports are available. Two of these cases (Walz (2) and Mylius and Schürmann (1)) were mentioned in the previous literature analysis but—for terminological reasons—they were not included in the tabulation of necropsies. One case (Stein (3)) had been overlooked.

We cannot, of course, be certain that no other autopsied cases have been reported in addition to the total of 18 plus 25 (that is, 43) which, after thorough search, we have been able to collect.

It seemed to us of particular importance to assemble all available case reports with autopsy findings because, as indicated in the 1938 literature report, many phases of sarcoidosis are quite inadequately known. Although the hypothesis of previous workers was advanced that sarcoidosis is a noncaseating phase of haematogenous tuberculosis, it was pointed out that many prominent workers disagree with this point of view and that no other than indirect evidence favors this aetiological concept.

Some of the clinical features of the disease need further elucidation, as well. The relevance, theoretical and diagnostic, of tuberculin anergy and of the so-called anticutins is still uncertain. The benignity of the disease has probably been overemphasized, considering the fact that about half of the autopsied cases died as a direct consequence of the disease, if one wishes to admit that caseating tuberculosis is one of the natural developments of sarcoidosis.

In any case, it is hoped that additional factual material will contribute not only to the knowledge but to a more complete understanding of the disease.

In addition to the 25 autopsy reports from the literature, one case of our own is presented which, because of the long and extensive clinical observations, seems to us to be particularly instructive.

CASE REPORT

M. de F., colored female, aged twenty-five, was admitted to the Montefiore Hospital on November 4, 1940. During her infancy the patient's mother died from tuberculosis and

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[1] From the Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, New York, New York.

her father from "pneumonia." She was a sickly but active child. In 1920, at the age of five, she was in a hospital for a month for the treatment of interstitial keratitis. In 1928, at the age of thirteen, she was operated on for hammer-toe. An X-ray examination of the chest, at that time, revealed "lung trouble," showing "marked enlargement of the paratracheal and hilar lymph nodes with some fibrotic and partially calcified nodules in the right infraclavicular region. The remainder of the lung parenchyma, including the apices, showed no evidence of gross mottling." In April, 1931, a month before she left the hospital, a film revealed "enlargement of the paratracheal lymph nodes" which showed a strong tendency to calcification. No conclusive evidence of active pulmonary tuberculosis was present. The Pirquet test was positive. The Wassermann test was negative. Sputum examinations did not reveal acid-fast organisms.

On her return home she felt well. At the age of seventeen (1932) she married. In 1934, 1935, 1936 and 1939 she was admitted to the Morrisania City Hospital for deliveries of full-term babies. On an additional occasion (1936) she entered the hospital for incision drainage of a breast abscess. X-ray films of the chest in 1935 and 1936 failed to disclose any abnormalities aside from calcifications at the left hilum (figure 1).

Her present illness started in the summer of 1937. She developed malaise and pain in the left side of her face. She soon noted a lumpy swelling behind the left ear and, a few weeks later, a similar swelling behind the right ear. She ran a low, intermittent fever. Later she experienced drowsiness, became thirsty and drank a great deal of water. At the same time she saw spots before her eyes and her eyelids felt droopy. She was admitted to the Morrisania City Hospital on November 3, 1937 and for the first time came to the observation of one of us (E. H. R.).

Physical examination revealed both parotid glands enlarged but not tender. There were palpable cervical lymph nodes. Both eye-lids were ptosed. The left pupil was slightly irregular with a corneal scar in front of it. Old maculae were present at the periphery of the right cornea. Laboratory findings revealed a moderate secondary anaemia. The Wassermann test was negative. An intracutaneous tuberculin injection of OT, 1:1000, did not produce any reaction. An X-ray film of the chest on November 5, 1937 (figure 2) disclosed marked enlargement of the hilar lymph nodes, as compared with the preceding film of January, 1936. A film taken a month later showed stippled infiltrations extending into the parenchyma, most accentuated in the mid-parts of the lungs. X-ray examinations of other parts of the body, including the skull and skeletal system, were negative. During her six weeks' stay in the hospital the swollen parotid glands receded in size, the temperature became normal and she improved subjectively. The clinical diagnosis was uveoparotid fever with neurological manifestations, as mentioned previously. The latter finding in this and in another patient with uveoparotid fever, who was under observation at approximately the same time, was the subject of a paper by Doctors Arbuse and Madonick (27) of the Neurologic Service of Morrisania City Hospital.

Following discharge from the hospital, the patient was under observation by the Board of Health and upon the advice of Dr. David Reisner was admitted to the Metropolitan Hospital for a short stay where biopsy was made of a cervical lymph node. The diagnosis was Boeck's sarcoidosis. She was readmitted to the Morrisania City Hospital in January, 1940, complaining of radiating pain in the lumbar region. She had nocturia, frequency and burning on urination associated with chills and fever. Urological examination disclosed a palpable right kidney which on X-ray examination was shown to have two pelves, calyces and ureters. Catheterized specimens revealed streptococci and *B. coli* on cultures. The pyelonephritis was presumed to be caused by sarcoidosis of the kidneys with secondary infection. A film of the chest revealed additional nodular infiltrations scat-

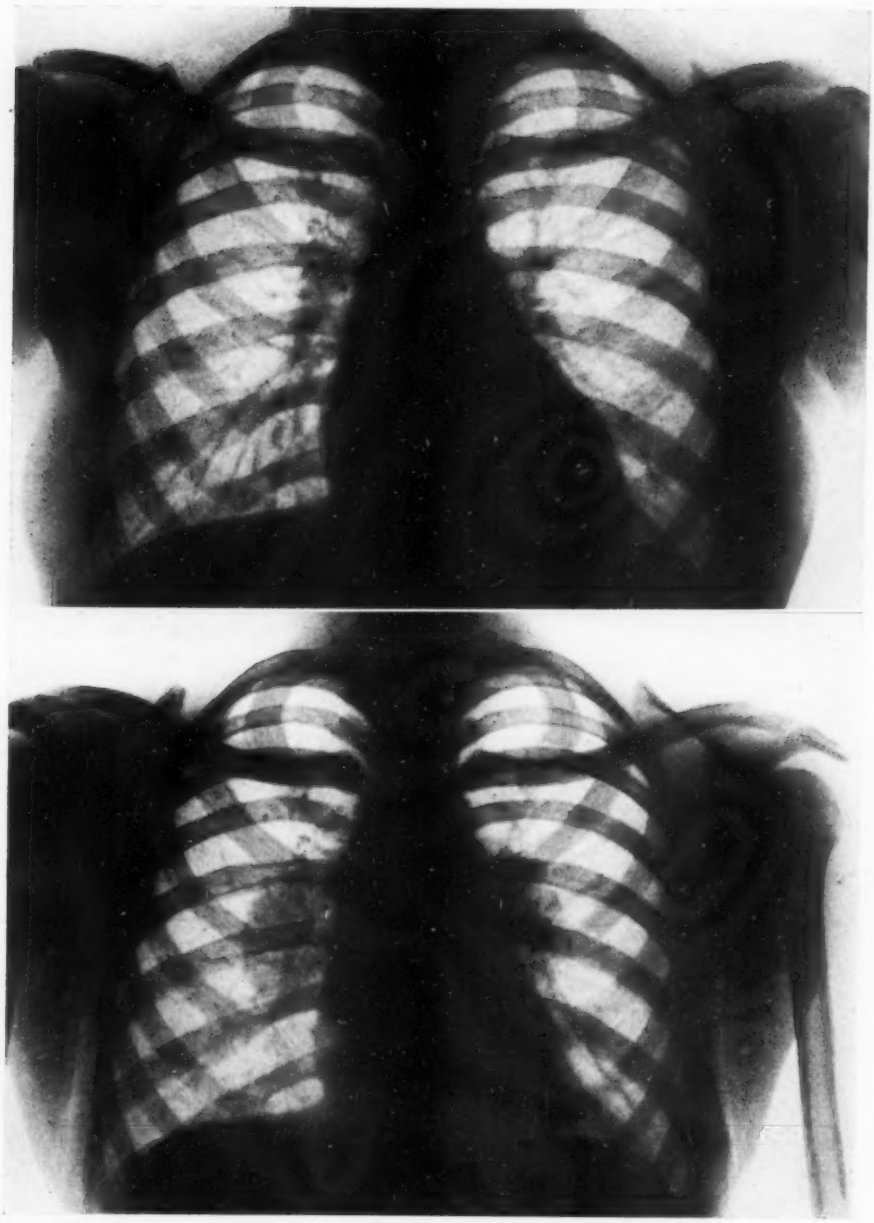

FIG. 1.(Upper) Roentgenogram, January 3, 1936 (Morrisania City Hospital). Small calcifications in hilar lymph nodes; no significant pulmonary findings.

FIG. 2. (Lower) Roentgenogram, November 5, 1937 (Morrisania City Hospital). Enlarged hilar lymph nodes bilaterally, more on the right. At this time, the patient had low-grade fever and bilateral parotitis.

tered throughout both lungs from apex to base. The patient improved subjectively and was discharged in February, 1940.

She was readmitted to Morrisania City Hospital in August, 1940 with the complaint that, since March of the same year, she had noted a mass in the left lower abdomen which gradually enlarged and a swelling that could be felt also on the right side. She had shooting pains in the abdomen, chills and fever. Examination revealed a large spleen and liver, the former extending from the left costal margin to the rim of the pelvis. Bone marrow smears showed no signs of any blood dyscrasia. Blood culture and agglutination tests for typhoid, paratyphoid, brucella and proteus were negative. Repeated examinations of the sputum were negative for tubercle bacilli. On August 30, 1940 peritoneoscopy was performed by Dr. Irving A. Sarot. A markedly enlarged spleen was seen. The surface was granular, purplish gray in color, suggesting a thickened capsule. No distinct nodules or tubercles were visible. There was no free fluid in the peritoneal cavity. A biopsy specimen of the spleen revealed, on microscopical examination, nodular accumulations of epithelioid cells with giant cells, some peripheral fibrous tissue and central caseation. The diagnosis was miliary tuberculosis. An X-ray film of the chest at this time showed a further increase in the extent of infiltrations in both lungs. In spite of blood transfusions and other supportive measures, the patient's disease progressed and she was transferred to the Montefiore Hospital on November 4, 1940 for further care.

The essential findings in the succeeding three months were as follows: She developed a generalized scaly eruption of the skin most marked on the legs, thighs and buttocks. Biopsy of a skin specimen revealed chronic granulomata with necrosis. The histological features seemed more consistent with those of papulonecrotic tuberculid than with Boeck's sarcoid. She developed a soft cystic mass over the eleventh rib in the right axillary line. Aspiration of the contents revealed purulent material in which many acid-fast organisms were demonstrated. This was the first occasion when these organisms were found. On one examination out of many, acid-fast organisms were also found on concentration of a gastric washing. X-ray films of the chest revealed an increase in the linear infiltrations in both lungs (the right lung is shown in the roentgenogram on the colored plate). Shortly after admission to the hospital she did not react to the intracutaneous injection of OT 1:1000; but the test was positive in the dilution of 1:10. Other laboratory tests revealed nothing significant. The patient was given radiotherapy over the region of the spleen for relief of pain, without success. She had continuous fever ranging from 99° to 103° F., chills, pain in the chest and dyspnoea up to the time of her death, February 17, 1941.

Autopsy Findings

The autopsy was performed by Dr. Virginia Lubkin. The organs and microscopical sections were reviewed by one of the authors (M. P.). The anatomical diagnosis was as follows: Generalized sarcoidosis of Boeck, terminating in wide-spread visceral tuberculosis. Tuberculosis of lungs. Old partly calcified tuberculous abscess right chest wall. Papulonecrotic tuberculids of legs (biopsy). Status post irradiation of spleen. Splenomegaly. Hypertrophy of right ventricle (slight). Ascites. Pleural effusion bilateral. Anomalous origin of both coronary arteries from single ostium. Bifid right ureter and pelvis. The brain and cord were not removed.

Lymph nodes: All the lymph nodes were enlarged. The parailiac, parafemoral, mesenteric and lower cervical nodes were firm, gray-pink, discrete and resistant to cutting. The retroperitoneal nodes, lying between the aorta and vena cava, and those along the splenic vein and at the splenic hilum were deep red and moderately soft. They produced very slight compression of the veins without invading them. The mediastinal nodes were

not conspicuous. The hilar and peribronchial nodes were enlarged. At the left hilum one enlarged node (2.5 cm.) was found, showing an area of calcification in an anthracotic, firm bed. The other nodes averaged 1 cm. in diameter and were imbedded in translucent slaty gray, hard tissue which fused with other hilar structures. The axillary, epitrochlear and upper cervical nodes were not examined.

Lungs: The left parietal pleura was slightly thickened and encrusted with flat grayish plaques, especially over the diaphragm. The right parietal pleura was thin and smooth. There were no intrapleural adhesions, except a few, firm, fibrous pleuropericardial bands. The visceral pleura on both sides was dull but thin, revealing an underlying heavy seeding with gray-green, firm plaques and nodules, 0.3 to 3 cm. in diameter. The lungs were firm noncrepitant throughout. They cut with considerable resistance, disclosing a universal dense dissemination of the same firm, somewhat translucent, irregular grayish nodules. They appeared to be composed of aggregates of pin-point to pin-head sized nodules, sometimes more than 1 cm. in diameter in aggregate. In the left lower lobe there was a 2 cm. area of firm caseation. There was no surrounding gross fibrosis. The intervening normal lung was aerated, soft and represented one-third to one-half of any given cut-surface. The upper half of the right upper lobe was occupied by many emphysema-

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PLATE I

Roentgenogram, November 8, 1941, of the right lung, showing considerable parenchymal involvement, as described in the text; the left lung showed essentially the same appearance.

Cut-surface of the right lung, showing fibrous bands, emphysematous blebs and small grayish-white nodular lesions of little more than miliary size.

Microscopical section (lower left) shows mainly cellular, but partly fibrosed sarcoid granulomata of miliary size in a lymph node.

Microscopical section (lower right) shows partly fibrosing sarcoid tubercles and emphysematous alveoli in the lung.

This color plate is reprinted from the series, "Major Pathology of the Lung, Series III," courtesy of Ciba Pharmaceutical Products, Inc.

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tous blebs, 1 to 1.5 cm. in diameter. The bronchi were pale, of average calibre and were surrounded by dense hyalinized, slightly bluish tissue described above and which appeared to extend from the hila along the vessels and bronchi for a short distance into the lungs. The pulmonary arteries were not involved (plate I).

Heart: The myocardium appeared brownish red, rather soft and contained minute yellow and grayish areas. There was an anomalous origin of both coronary arteries from a single ostium.

Liver: It weighed 1,800 g. and was moderately firm and revealed six soft nodules on cut-surface (figure 3), measuring 3 to 12 mm. in diameter, consisting of thick greenish or yellow purulent material surrounded by firm white capsules. Direct smear from one of these areas showed many acid-fast bacilli. Inoculation into a guinea pig and culture of this material proved the presence of tubercle bacilli.

Spleen: The organ weighed 1,300 g. and measured 27 x 16 x 7 cm. It was very hard. The capsule was slightly thickened. The cut-surface appeared blackish red and slightly granular. On the medial edge, about 2 cm. below the splenic notch, a white nodule projected, measuring 1.5 cm. in diameter (figure 3).

Kidneys: Each weighed 230 g. The capsules were slightly thickened but stripped easily, leaving a smooth surface which showed innumerable, evenly scattered pin-point

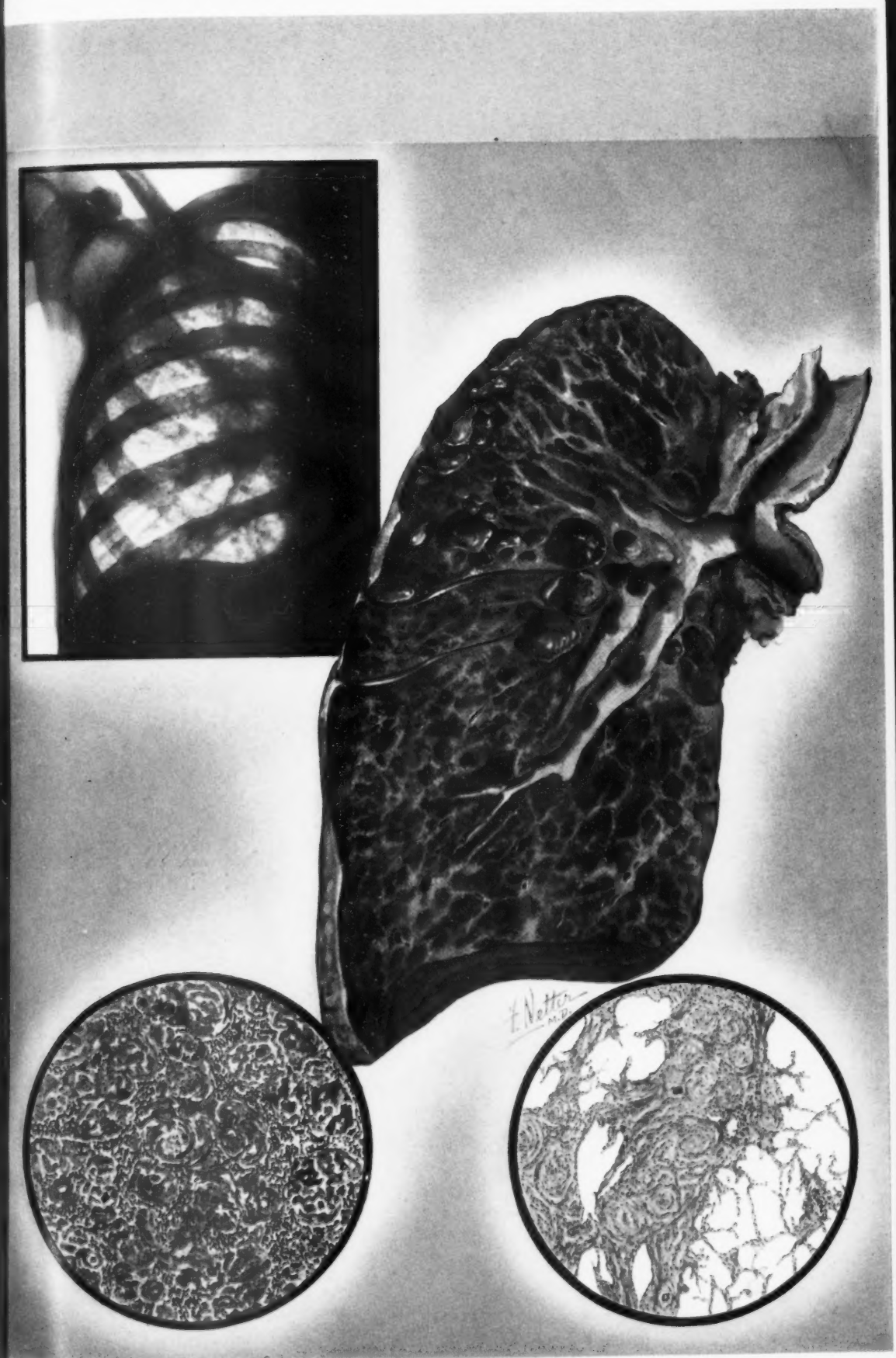

PLATE 1

haemorrhagic spots. In addition there were a few firm yellow nodules, measuring 1 mm. in diameter, slightly projecting over the smooth surface. On cut-surface, there was a fairly dense seeding of flat, grey, translucent nodules, measuring from 0.3 to 2 mm. in diameter. The right kidney had an extrarenal, bifid pelvis with a bifid ureter (figure 3).

All other organs did not show any pertinent gross changes.

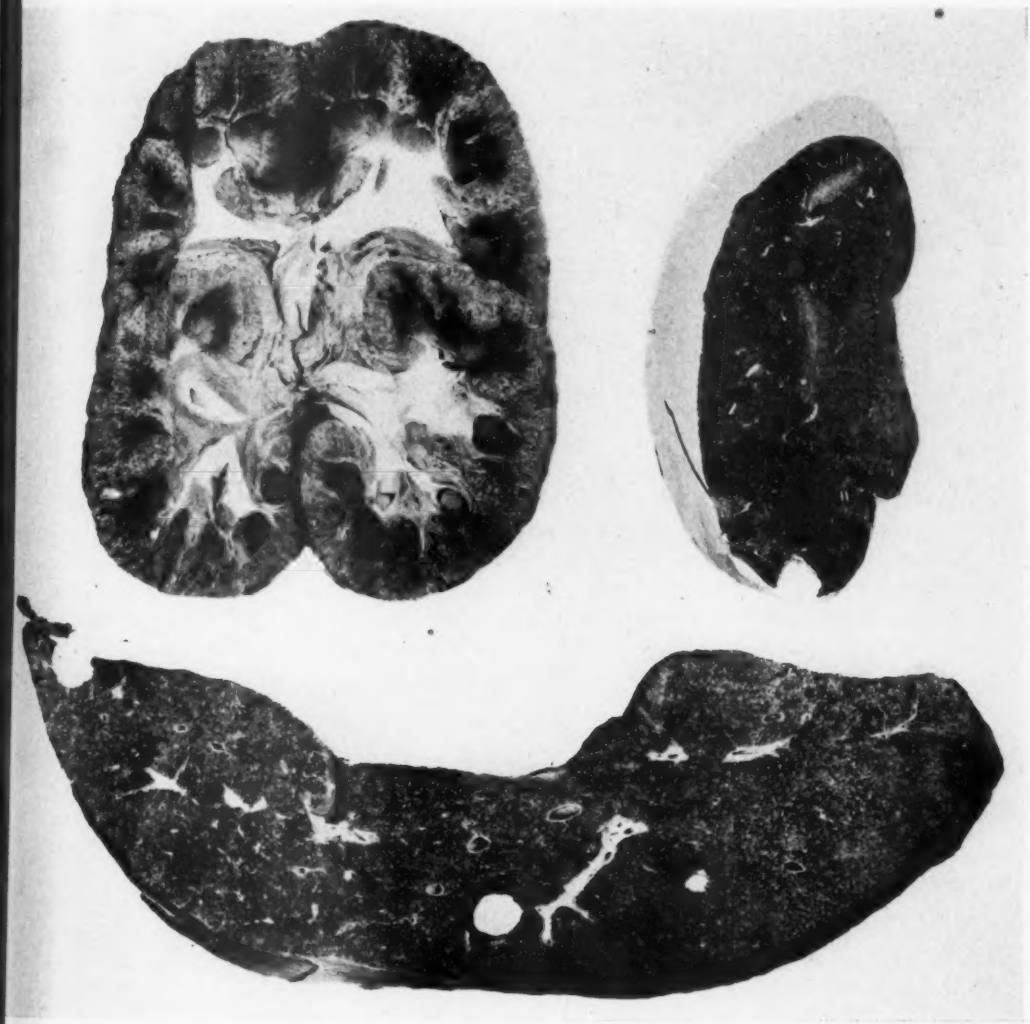

FIG. 3. The cut-surfaces of liver, spleen and kidney are shown, as described in the text.

The essential findings on microscopical examination were as follows:

Heart: There is a slight perivascular fibrosis, slight thickening of arteries and considerable fraying and degeneration of muscular fibres.

Lungs: Sections from the right upper lobe show marked alveolar emphysema with fibrous thickening of alveolar walls and septa. The smaller and smallest bronchi are

somewhat dilated but do not show any morphological evidence of infection. Scattered in rather dense and even seeding, epithelioid tubercles of miliary size are seen; they contain few Langhans giant cells and no or minimal caseation (see right lower section on colored plate). The fibrosis is hyaline, particularly in perivascular and peribronchial spaces and encloses a few minute calcified bodies of homogeneous structure. Sections from the right lower lobe reveal essentially the same findings, but both emphysema and fibrosis are less marked. In addition, a few conglomerate, caseating tubercles are seen and a few small patches of large-cell tuberculous pneumonia. Both noncaseated and caseated tubercles contain some giant cells, but only those in the former contain occasional calcified bodies, some of which are ring-shaped. The left upper lobe shows histological changes similar to those in the right upper lobe. Many completely fibrosed granulomata are present. The epithelioid cell tubercles contain giant cells and many of the latter enclose small calcified bodies, many of which are stained dark blue by Weigert's elastica stain. The left lower lobe is distinguished from the other lobes only by the presence of large areas of tuberculous pneumonia, both in its purely cellular and its caseated phase.

Liver: There are many noncaseated epithelioid granulomata, most of which are located in the portal spaces. Many of them show various degrees of peripheral fibrosis. One tuberculous abscess is seen, the wall of which shows epithelioid granulation tissue.

Spleen: The normal architecture is hardly recognizable, mainly because of the almost complete absence of lymph follicles (effect of X-ray radiation?). There appears to be a diffuse proliferation of monocytic cells of the epithelioid type. There is a dense seeding of miliary epithelioid granulomata, some with, and some without central caseation (see left lower section on colored plate). One subcapsular area of caseation with central liquefaction is present; it is surrounded by hyaline fibrotic tissue.

Kidneys: The left kidney contains a few miliary caseous tubercles; the right shows two larger caseous tubercles near the pelvis. There are a few mainly epithelioid tubercles in the cortex. The convoluted tubules show severe degenerative changes with cellular necrosis and their lumina contain albuminous material, cellular debris, casts and blood. There are irregularly distributed interstitial fibrosis and oedema and occasional small calcified bodies. Some glomeruli are shrunken and fibrotic.

Diaphragm: On the serosal surface is a layer of tuberculous granulation tissue with little caseation.

Vertebra: The marrow contains many calcified and fibrosing granulomata, some of which show typical sarcoid structure, while others contain areas of caseation.

Breast: A section reveals epithelioid tubercles with a few giant cells and a hyalinized tubercle suggestive of a healed sarcoid lesion.

Lymph nodes: The peribronchial lymph nodes reveal hyalinization with caseous and calcified foci. The mediastinal nodes are almost completely hyalinized and contain a few calcified foci suggestive of primary lesions. In the paraäortic and mesenteric lymph nodes there are caseated as well as noncaseated tubercles, some suggestive of healed tubercles in various stages of hyalinization.

Adrenals: These organs contain many, apparently young caseating miliary tubercles.

Nothing remarkable is found in the other organs (uterus, ovary, thymus, thyroid, parathyroid and pancreas).

Tissues stained by the Ziehl-Neelsen method reveal the following: Acid-fast bacilli are readily demonstrated in the caseated lesions in the lungs, liver, kidneys, vertebra and adrenals. In more than 50 noncaseated, epithelioid cell tubercles in the lung, liver and spleen, no acid-fast bacilli could be found. The search for acid-fast bacilli in lymph node lesions was entirely unsuccessful.

Summary of Case Report

The history of the patient extended over a period of twenty years, from the age of five to the time of death, at the age of twenty-five. The evolution of the disease covered four distinct phases:

1. A period of primary infection, confirmed by X-ray examination and positive tuberculin test.

2. An interlude of good health during which time the patient married, bore four healthy children without symptoms or roentgenological signs of pulmonary disease.

3. The development of noncaseous tuberculosis in the form of uveoparotid fever, pulmonary sarcoidosis, generalized adenopathy and biopsy confirmation of sarcoid tubercles in a lymph node. During this period she failed to react to 0.1 mg. of OT.

4. A final phase of transformation of noncaseous to caseous tuberculosis, evidenced first by the finding of caseous tubercles in the spleen, later by papulonecrotic tuberculosis of the skin, tubercle bacilli in a subcutaneous abscess and finally in generalized tuberculosis. Even during this final phase of the disease she reacted only to 10 mg. of OT.

AUTOPSY REPORTS FROM THE LITERATURE

In a previous paper (26), reports of 17 autopsies were tabulated with the addition of one case observed by the author. In the same paper, the case, reported by Mylius and Schürmann, was mentioned, but not included in the list of autopsy reports on sarcoidosis, because of the particular nomenclature used by these authors. In the following pages, all autopsy reports that have come to our knowledge since and those that have been overlooked in the previous paper, are briefly described, bring the total of autopsied cases up to 43.

(1) *Mylius and Schürmann:* The patient, a man of twenty-five years, developed a severe inflammation of the eyes so that one had to be enucleated in 1925. The remaining eye was found to have tuberculous iritis. In 1926, he developed Boeck's sarcoidosis of the skin. In 1924 he developed swelling of the fingers and X-ray examination showed many cystic formations in the distal ends of the phalanges. His general condition was good until 1926 when he developed dyspnoea but no cough or expectoration. An X-ray film of the chest in early 1926 revealed bilateral enlargement of the hilar shadows and dense infiltrations in the pulmonary parenchyma on both sides. At first, he had periodic fever; later, the fever became high, pleuritis, ascites and oedema developed and he died in 1928 of cardiac failure.

During 1926 the Pirquet tuberculin test was positive. Later in the disease, tuberculin testing was negative both to human and bovine tuberculin. Guinea pigs and rabbits were inoculated with material from the skin, soft structures of the fingers, blood and sputum. The animals were sacrificed six months later without revealing specific changes in the organs.

Autopsy: The pertinent gross findings were: skin lesions, as described clinically; right cardiac hypertrophy; fibrous induration of upper lobes of lungs, ectatic alveoli, disseminated gray-green small nodules and a few acinous and two hazelnut-sized liquefied caseous foci; massively enlarged, firm, noncaseated lymph nodes in the mediastinum and in the

portal region; firm, enlarged spleen (weight 350 g.); three pea-sized stony foci in the mesentery. All other organs appeared normal.

On histological examination submiliary and miliary foci were found, composed of epithelioid cells with lymphocytic borders, some without, some with few giant cells and band-like and nodular foci of hyaline connective tissue. The latter type of tissue change was particularly dominant in the lung and lymph nodes, whereas in the liver and spleen only cellular foci were seen. Central caseation was noted in some of the granulomata in the liver, spleen, very rarely in the lymph nodes and in the bone marrow. Caseation was absent in the skin lesions and in the granulomatous and hyaline foci around the pericorneal vessels, in the iris, in the ciliary body and the chorioidea. In addition, banal caseous tubercles were present in the lung. In all sarcoid foci, occasional minute calcific deposits were seen in giant cells and embedded in hyaline tissue. Particular mention is made of the fact that the hyaline tissue stained in part red and in part yellow with van Gieson stain.

No acid-fast bacilli or granula were seen in the sections. Material from mediastinal nodes was injected into 3 rabbits which were found to be normal six months after inoculation. Of 5 guinea pigs similarly inoculated, 3 remained alive while 2 died of inoculation tuberculosis in two and four months, respectively. No acid-fast bacilli could be recovered by culture from the mediastinal nodes, but cultures from the involved organs of the tuberculous guinea pigs yielded typical human type tubercle bacilli.

(2) *Mylius and Schürmann* give the postmortem findings of a case reported previously by *Walz*.

The patient, a man of fifty-two, had hilar lymph node enlargement as a child. From the age of twenty-two to thirty, he had morning cough and slight expectoration. At the age of thirty-five he developed a right-sided exudative pleurisy and one-half year later X-ray examination of the chest revealed changes in both apices, right-sided pleurisy and large tumefactions in the mediastinum. Repeated Pirquet and intracutaneous tuberculin tests with OT were negative to as much as 5 mg. Tubercle bacilli were found in the sputum and pleural exudate.

Sixteen years before he died, an operation was performed and lymph nodes, the size of a man's fist, were removed from the mediastinum. Lymph nodes which were matted to the aorta, large veins and trachea and those deep in the mediastinum were not removed. The patient felt well for ten years thereafter. Then, he became increasingly more dyspnoeic. X-ray examinations in the latter five years of his life showed a gradual increase in the size of the mediastinal lymph nodes.

Biopsy report by Walz: A mediastinal tumor mass was excised. The total weight was 605 g. On histological study it was found to contain many small foci of epithelioid cells with Langhans giant cells and few lymphocytes along the margins of the epithelioid foci. These foci were surrounded by massive connective tissue, part of which was hyaline. There was no caseation and no acid-fast bacilli were seen. Walz stated that the most likely diagnosis was tuberculosis of lymph nodes. He emphasized the unusual features of the enormous development of connective tissue and the complete absence of caseation.

Autopsy report by Mylius and Schürmann: The autopsy was limited by a thoracic incision. The lymph nodes in the mediastinum were swollen to the size of a man's fist and extended down to the diaphragm. They were firm and had a smooth, flesh-colored cut-surface with irregular gray-green spots. The lungs showed some fibrotic shrinkage of the apical portions. The cut-surfaces presented gray-green indurations, ectatic alveoli and emphysematous bullae. Histologically, both lymph nodes and lung tissue showed only epithelioid tubercles and hyaline nodules and strands. There was no caseation and

no acid-fast bacilli were found. The tissue was neither cultured nor inoculated into animals.

(3) *Stein:* The patient, sixty-eight years of age, was admitted to the hospital on November 1, 1926. Her husband had died from tuberculosis. Nine of her 13 children had died, one of them from tuberculosis at the age of five months. The patient became ill three and a half years previously when she noted a small wound in the skin. A month later nodules appeared on the forehead, face and other parts of the body. On admission to the hospital examination revealed enlarged axillary and cervical lymph nodes. Pale violet nodules of varying size were present on the face, breast, abdomen and other parts of the body. The lungs revealed arrested fibrotic tuberculosis in the right upper lobe and pulmonary emphysema. Radiographic examination of the chest confirmed the presence of a cirrhotic process below the clavicles. The Pirquet test was negative on two examinations. The Mantoux test was practically negative. The blood revealed 12 per cent monocytes. The anticutin reaction was positive. Noteworthy was the finding that the tuberculin reaction turned positive following a course of tuberculin treatment. The patient developed hemiparesis and died January 22, 1927.

The autopsy revealed many skin lesions over the face, body and extremities. The lungs showed old apical and bronchial tuberculosis and hypostatic pneumonia. In addition, there was atherosclerosis; myofibrosis of the left ventricle; thrombosis in region of optic thalamus and haemorrhage in the pia of the cerebellum. Histological examination disclosed epithelioid tubercles in the skin without acid-fast bacteria. There were no similar lesions in any other organs.

(4) *Wahlgren:* A woman, fifty-nine years of age, had influenza with pneumonia in 1920. The following year she experienced cough, abundant expectoration, dyspnoea, fatigue and loss of weight. The diagnosis was chronic interstitial pneumonia with bronchiectasis. Many sputum examinations failed to reveal acid-fast organisms. A Mantoux reaction in 1932 was negative with 1 mg. tuberculin and in 1936 with as much as 3 mg. In the spring of 1936, she developed progressive heart failure and died.

Autopsy revealed both lungs attached to the upper thoracic walls by adhesions. The rest of the pleurae were free although thickened. The left upper lobe was firm. On section, the tissue was gray, markedly indurated and with a greasy shine. At the apex, smooth-walled cavities were found. The bronchi were somewhat dilated. The left lower lobe contained a finely-meshed network of narrow, gray-colored streaks, showing anthracotic pigment. The right lung presented essentially the same picture, but the cavities in the upper portion were less numerous. The spleen was enlarged, the surface covered by grayish nodules ranging in size from pin-heads to hemp seeds. The lymph nodes at the hila of both lungs along the sternum, along the carotid and abdominal aorta, as well as in both axillae and inguinal regions were moderately enlarged and on cut-surface appeared grayish-red. Roentgenograms of the hands and feet taken at autopsy revealed alterations in the form of circumscribed, decalcifications of several phalanges. The other organs showed nothing remarkable.

Histologically the disease was characterized by the presence of clusters of epithelioid cells which closely resembled tubercles. Small necrotic areas were sometimes seen in these clusters, but on the whole the agglomerations showed a distinct tendency to fibrous induration and many underwent transformation into markedly hyalinized, cell-containing connective tissue. Some giant cells, mostly of the Langhans type, were seen. In the lungs, the process had the characteristics of a chronic interstitial pneumonia with marked tend-

ency to induration and shrinking. The peribronchial tissues were thickened and often hyalinized. In the spleen, epithelioid cell nests were found in the follicles as well as in the pulp. A series of guinea pigs were inoculated with tissues from the lungs, spleen and lymph nodes. None of the animals had developed tuberculosis at the end of three months.

(5) *Berg and Bergstrand:* A man of twenty-five developed a low-grade fever in 1936. X-ray examination disclosed hilar lymphadenitis. In the course of the year he was admitted twice to a hospital. On the second occasion, in May–June, 1936, there were found, in addition to the hilar lymphadenitis, swollen cervical lymph nodes. The latter gradually increased in size. An excised node revealed an appearance of atypical tuberculosis. Physical examination showed nothing remarkable. The sputum did not contain tubercle bacilli. X-ray examinations of the chest showed increase in the size of the hilum and paratracheal lymph nodes with massive infiltrations, extending into the pulmonary parenchyma on both sides. The Mantoux reaction was negative up to 0.1 mg. of OT; it was weakly positive to 1 mg. A nut-sized submandibular lymph node revealed on histological examination probable sarcoidosis with minimal necrosis. There was a monocytosis of from 1 per cent to 23 per cent. Throughout his illness he had a low-grade fever, slight loss of weight, moderate cough and increasing dyspnoea. Later in the disease, the patient developed conjunctivitis and symptoms referable to the nervous system. Death resulted from increasing stupor and cardiac failure.

Autopsy: Gross examination revealed hyperaemic and oedematous lungs; large and firm mediastinal lymph nodes without calcification or caseation; a much enlarged, firm spleen, containing enlarged lymph follicles and markedly enlarged retroperitoneal lymph nodes.

The histological examination showed a fibrino-polynuclear pneumonia. In addition, the lung contained epithelioid tubercles with much reticular tissue, without caseation and some giant cells. In the latter, inclusion bodies were seen, some of which were calcified. The inner core of the bodies consisted apparently of elastic fibres. Spleen and lymph nodes were seeded with epithelioid tubercles, many of which showed central caseation.

Bacteriological studies on autopsy material are not reported.

Of 19 illustrations in the report, not one shows a section on which a diagnosis of sarcoidosis could be based. However, the authors are undoubtedly familiar with sarcoidosis and it may be assumed that, at least, some of the lesions, particularly in the lung, were of characteristic sarcoid structure.

(6) *Nieuwenhuijse:* A woman of thirty was admitted with a history of cough, expectoration and fever of a few days' duration. Although the cough and expectoration ceased, roentgenological examination disclosed extensive pulmonary lesions. Both lungs, the lower and mid-fields particularly, exhibited dense crops of very small, partly blurred foci without cavitation. The hilar and paratracheal lymph nodes were appreciably enlarged. The Pirquet and Mantoux tests were negative. Tubercle bacilli could not be cultured from the gastric contents and urine. A lymph node removed from the left supraclavicular region disclosed large-celled and some fibrotic and hyaline tubercles. Caseation and tubercle bacilli could not be demonstrated. A diagnosis of Besnier-Boeck's disease was made. The patient suddenly developed acute fat necrosis, associated with severe peritonitis to which she succumbed within two days despite prompt operation.

Necropsy disclosed areas of necrosis in the pancreas with diffuse fat necrosis in the abdomen, as well as extensive lesions of the respiratory organs. There were also found several nodules in the spleen and a solitary focus in the liver. No abnormalities were

found in any of the other organs. The lungs revealed countless very small, round nodules whose grayish-white color contrasted sharply against the red lung tissue. The nodules were unevenly distributed in the mid-portions of the lungs following the course of the bronchi, blood and lymph vessels. Many of the nodules projected into the lumina of the bronchi and even into the trachea. There were no caseous foci, cavities, calcified areas or scar tissue as evidence of a primary tuberculous process. The lymph nodes at the hilum and trachea were appreciably enlarged but were not caseous. The costal and visceral pleurae were largely covered with thick, confluent, flat nodules in a mould-like manner.

Microscopical sections disclosed noncaseating tubercles with a tendency to form fibrous tissue undergoing hyaline degeneration. Tubercle bacilli could not be demonstrated by rabbit and guinea pig inoculations.

(7) *Spencer and Warren:* The patient, fifty-one at the time of death, was well up to the age of thirty-four, when he had "neuritis" and at forty-three he had appendicitis. In May, 1934, he developed pain, swelling and stiffness in the hands and feet, progressive anaemia, loss of weight, weakness and cough. Physical examination revealed fusiform swellings of the fingers and wrists and oedema of the ankles. There was a generalized peripheral lymph node enlargement. An X-ray film of the chest disclosed dense symmetrical, bilateral enlargement of the hilar nodes and fine lace-like infiltrations, extending out from both roots into the parenchyma. X-ray films of the skeletal system showed hypertrophic changes about the dorsal and lumbar vertebrae. A doubtful reaction was obtained in gonococcus complement fixation. Roentgen therapy over the chest did not influence the hilar lymphadenopathy. At the time he came under observation of the authors, the gonococcus complement fixation test was positive. Physical examination now revealed oedema of the ankles and fusiform swellings of the phalangeal joints. The peripheral lymph nodes were no longer enlarged. He developed signs of duodenal ulcer which, in 1935, necessitated a posterior gastro-enterostomy. An X-ray film of the chest did not reveal the hilar lymph node enlargement seen previously. Later films, however, showed a picture similar to the original one and a diagnosis of sarcoidosis was made. Still later in the disease he developed erythematous patches over the forearms which were not characteristic of Boeck's sarcoid. Laboratory studies, aside from the positive gonococcus complement fixation, were negative. The tuberculin test gave no reaction. One week prior to death he developed oedema of the larynx and died with symptoms of air hunger and collapse.

Autopsy: The lungs were voluminous. There were no adhesions. On section, the lobes were firm, pinkish-gray and contained nodules, 3 mm. or less in diameter, which were firm and black. A healed primary tuberculous complex was found in the lung. There were duodenal and jejunal ulcers (with old posterior gastro-enterostomy). Oedema was present in the larynx and trachea.

Microscopical examination showed numerous miliary lesions which were typified by small collections of epithelioid cells with infrequent multinuclear giant cells. There was no caseation. The lesions were discrete and frequently surrounded by collagenous connective tissue. Sarcoid lesions of similar structure as in the lungs were found in the bronchopulmonary, tracheal, paravertebral, iliac and inguinal lymph nodes, trachea, heart, spleen, liver, thyroid gland, kidneys and skin.

(8) *Naumann:* On November 20, 1936 a three-month old infant was admitted with severe anaemia and high fever. The child had fallen ill two days previously with restlessness

and profuse sweating. Examination revealed enlargement of the liver and spleen. The heart and lungs were normal. There were present a Jaksch-Hayem type of anaemia, signs of meningeal irritation, nodules in the skin and changes in the eye grounds. The Wassermann and tuberculin (1 mg.) reactions were negative. In the following six weeks the infant developed haemorrhagic tendencies and several blood transfusions were given. The fever continued and the urine contained pus. A nodule removed from the skin revealed nonspecific granulation tissue. The child died with symptoms of asphyxia.

The autopsy disclosed a large liver; slight splenic tumor; large gray nodules in enlarged kidneys. Some nodules were found in the stomach wall, periportal lymph nodes and under the serosal covering of the urogenital tract, subdurally in the falx and tentorium cerebelli, underneath the bones of the calvarium and in the choroids of both eyes. The lungs were normal. The diaphragm was pushed high by enlarged abdominal organs.

Histological examination disclosed that the nodules seen on gross examination in the various organs were sarcoid lesions. The final diagnosis was: diffuse, sarcoid, atypical lymphogranulomatosis.

(9) *Berblinger:* A twenty-five year old patient developed bilateral iridocyclitis in January, 1938. It was suspected to be tuberculous because of the associated presence of enlarged hilar lymph nodes according to X-ray examination. On admission to a sanatorium, an X-ray film of the chest still showed the hilar lymphadenopathy but no changes in the pulmonary parenchyma. A tuberculin test was not done. He developed gingival bleeding and bleeding in the skin; at this time there were practically no thrombocytes. He suddenly developed an apoplectic stroke with paralysis of the facial nerve and right side of the body and died.

Autopsy: The diagnosis of essential thrombocytopenia with cerebral haemorrhage as the immediate cause of death was confirmed. In addition, epithelioid and lymphocytic tubercles with few giant cells and no caseation were found in the lungs, spleen, liver, tongue and in the massively enlarged lymph nodes of the mediastinum. The tubercles showed considerable amounts of fibrillar connective tissue, along the margin of which epithelioid tubercles were found. Miliary epithelioid and lymphocytic tubercles were scattered throughout the interstitial pulmonary tissue and in the bronchial walls.

No tubercle bacilli could be found in the sections. However, lymph node material was injected into guinea pigs. The injected animals were killed six weeks following inoculation. In one of the animals, one epithelioid tubercle was found in a lymph node. Spleen and lymph nodes of the first injected guinea pigs were transferred into new guinea pigs which developed typical inoculation tuberculosis. From the second series of animals a human type tubercle bacillus was isolated.

Berblinger points out that the histological findings in his patient are identical with those reported by Mylius and Schürmann, that they correspond to the lesions that v. Recklinghausen called Schüppel's lymphoma and to those that Ziegler described as large-cell tuberculous hyperplasia.

We believe that Berblinger's case is the only one on record from which a tubercle bacillus was isolated and identified, although no caseation was seen in any of the tubercles examined. However, why isolation of bacilli was possible only in the second series of animals remains unexplained, unless one assumes that the first series of animals was killed too soon following inoculation.

(10) *Courmont, Gaté and Gardère:* A man of thirty-five, when an infant, was in a preventorium with tracheobronchial lymphadenopathy and a positive tuberculin reaction. At

the age of eleven, he had pneumonia; at the age of thirty-two, bronchitis. The onset of the present illness was in October, 1935 when he developed grippal symptoms with fever and loss of weight. X-ray examination revealed nodular infiltrations in the mid-portions of both lungs which did not resemble tuberculosis. In addition, there were present discrete nodular skin lesions of a roseate papular appearance, one at the angle of the right eye and several on the forearm. His temperature continued subfebrile but the general condition of the patient was good. He did not cough and had little sputum which did not contain acid-fast organisms on repeated examinations, as well as on guinea pig inoculations. The skin lesions progressed. Biopsy of a specimen from the skin and from an epitrochlear lymph node revealed sarcoidosis. The patient developed subacute nephritis and albuminuria. Death resulted from a pulmonary haemorrhage.

At autopsy, the right lung was found congested and contained many hard nodules. A soft nodular lesion was found in the upper part of the upper lobe. It was said not to be caseous but looked caseous. Material from this part was used for guinea pig inoculation. The nodules looked more like metastatic carcinoma than tubercles. Similar nodules were present in the left lung. The source of the haemorrhage was not found. The lymph nodes were small and dark. The kidneys were enlarged, cyanotic and contained many whitish granulations of millet size. Each adrenal contained one nodule the size of a small nut. No gross changes were noted in the other organs.

Histological examination of the skin revealed epithelioid cell accumulations with many lymphocytes and some plasma cells and some fibrosis. A nodule in the left lung revealed a necrotic centre with obliterated vessels. The cellular part was composed of epithelioid and lymphoid cells without giant cells. Similar lesions were found in a section below a pleural thickening. No specific lesions were found in the hilar lymph nodes. The left kidney contained interstitial foci, composed mainly of lymphocytes. (The description does not suggest sarcoidosis.) In the left adrenal the normal structure was absent. The nodule in the substance consisted of a portion of degenerated tissue and a portion of cellular infiltration composed of lymphocytes and "cells of connective tissue with acidophile protoplasm and very rare plasma cells," the former cells are called *d'aspect epithélioide*. Some cells look like young Sternberg cells. According to the authors, "the anatomopathological findings confirm with certainty the clinical diagnosis of Besnier-Boeck disease."

The pertinent laboratory findings were as follows: All serological reactions were negative. Specimens of sputum on smear, culture and guinea pig inoculation were negative for acid-fast organisms. Animal inoculation of urine, blood and biopsy tissue were also negative. Tissues from the necrotic lung focus inoculated into rabbits subcutaneously produced at the site of inoculation fibrocellular nodules *reticulose folliculaire avec necrose centrale*, not tuberculous. This tissue yielded no growth on Loewenstein's medium. Guinea pig inoculation with material from the necrotic lung focus was negative. Negative results were also obtained from inoculations in rats and monkeys. From the pulmonary focus several microcultures of polymorphous appearance were obtained. In one subculture there were acid-fast bacilli, somewhat thicker than tubercle bacilli; on subculture they were not acid-fast. The authors believe that only the very polymorphic organism obtained in microcolonies is the specific causative agent, but no attempt was made to show that the different forms belonged to the same species. The clinical course was very atypical.

(11) *Cotter:* The patient, a Negro of eighteen, gave a history of progressive fatigue, loss of weight, dyspnoea, oedema of the ankles and cough. Physical examination revealed a dyspnoeic man with evidences of right ventricular cardiac failure to which he succumbed

about a month after admission to the hospital. An X-ray film of the chest disclosed heavy thickening of the hilar structures of each lung with infiltrations radiating to the periphery and base. Laboratory findings revealed strongly positive Wassermann and Kahn tests. The skin reaction to 0.1 cc. of OT (1:100) was negative after forty-eight hours.

Autopsy: The body was undernourished. The superficial lymph nodes were enlarged. The heart was hypertrophied; the muscle bundles distorted by numerous irregular opaque yellowish areas which occupied a considerable portion of the myocardium. Small nodules were present beneath the endocardium and on the contact surface of the aortic leaflet of the mitral valve. The lungs were heavy. A number of nodules of varying size were present in the parenchyma which on cut-surface had a gray opaque appearance.

Microscopical examination revealed the lesions to be composed of multiple, discrete, tubercles, composed of endothelial cells, often associated with a giant cell and surrounded by a thin layer of lymphocytes. The unusual degree of myocardial involvement was noteworthy. In addition to the heart and lungs, sarcoid changes were present in the lymph nodes, spleen, testicle, wall of the alimentary tract and in a subcutaneous nodule removed from the left forearm. No signs of caseous tuberculosis were discovered in any of the organs.

(12) *Bergmann:* The report concerns two sisters. The older one of the two was admitted with a diagnosis of bilateral, chronic haematogenous tuberculosis and died eventually of right heart failure. She was examined at autopsy and the report deals mainly with this case.

The younger sister also was considered to have had chronic haematogenous tuberculosis and she, too, died of right heart failure. But autopsy was not done. However, the clinical course of the disease in both instances was so alike that it is possible that both sisters suffered from the same disease: Boeck's sarcoidosis. The younger sister revealed, during life, enlargement of the spleen, sarcoidosis of the skin, tuberculous skin abscess and conjunctivitis. The sputum was always free from tubercle bacilli. Intracutaneous tuberculin gave a moderately positive test.

The history of the older sister, aged twenty-seven, is as follows: In March, 1931 she developed "encephalitis" and "rheumatic arthritis." By the end of May, she was out of bed but was dyspnoeic. An X-ray film taken at this time revealed many miliary infiltrations in both lungs, more marked in the right. The hilar lymph nodes were enlarged. The diagnosis was miliary tuberculosis. Despite the extent of the lung involvement, auscultation did not reveal any abnormal signs. There was no fever, no cough or expectoration. Intracutaneous tuberculin (human type) did not cause any reaction. An X-ray film of the chest in August, 1931 revealed widening of the mediastinal shadows on both sides. The hilar shadows were enlarged, particularly on the right with many fine infiltrations involving the mid-lung region, simulating miliary tuberculosis. The course of the disease was characterized by increasing dyspnoea, first by marked gain, later by marked loss of weight. The sputum never revealed tubercle bacilli. X-ray films of the chest on later occasions revealed an increase in the hilar shadows on both sides and beginning cavitation in the right mid-lung field and later cavitation at the base of the left upper lobe. For a time she was ambulant. In June, 1933, she became less dyspnoeic but developed a small subcutaneous abscess in the left upper dorsal region from which 10 cc. of pus were aspirated. The abscess healed. Roentgenograms of the chest showed no significant changes. In 1934, X-ray films of the chest revealed an increase in the densities in both lungs with signs of breaking down. In 1935, a cold abscess appeared in the right

epigastrium. The condition gradually became worse, the dyspnoea and cyanosis increased. She developed Boeck's sarcoidosis of the skin. Death resulted from cardiac insufficiency, in July, 1938.

Autopsy: On postmortem inspection, the skin lesions, as reported clinically, were noted. The lungs were emphysematous and many noncaseated tubercles were present on the pleurae and there were deep scar retractions. The shrunken left lower lobe contained much slate-colored, gray-green indurated tissue. Occasional miliary tubercles were scattered through the lungs. Both cardiac ventricles were dilated and the right side of the heart was hypertrophied. The mesenteric, portal, pancreatic, paraäortic, cervical, supraclavicular, mediastinal, peribronchial and bifurcation lymph nodes were enlarged, the latter measuring 8 x 5 x 5 cm. The cut-surface of the nodes was flesh-like and there was no caseation. The spleen was large (370 g.), firm and contained many miliary nodules and small follicles. In the lower half of the jejunum and in the ileum there were many ulcers, measuring 1 to 2 cm. in diameter; some of them were scarred. Similar, but larger ulcers were present in the caecum. Small groups of gray miliary tubercles were seen on the serosal surface overlying the ulcers. Each adrenal contained a caseous nodule of 1 cm. in diameter.

On histological examination, epithelioid tubercles with some lymphocytic borders were found in the spleen, in the interstitial and capsular tissue of the liver, in all lymph nodes and in the pulmonary parenchyma. In the latter two sites there was massive hyalinization of lesions. The adrenal foci showed caseation and sclerosis. The intestinal ulcers were apparently tuberculous. The skin lesions did not show any specific structure, but they contained some hyaline sclerosis. Cultures from hilar nodes and lung tissue yielded tubercle bacilli of bovine type.

(13) *Capuani:* The history is that of a forty-four year old cabinet maker. In 1930 he developed swelling of the lymph nodes of the entire body. One year later he began to cough, expectorate and had fever. In 1936 a diagnosis of pulmonary tuberculosis was made. Late in that year he came to the observation of the author at which time he complained of dyspnoea, cough and expectoration. Physical examination disclosed generalized adenopathy and signs of upper lobe involvement. The sputum was negative for tubercle bacilli. An X-ray film of the chest revealed findings which were considered as caused by fibrocaseous tuberculosis. From October, 1936 to March, 1938 repeated sputum examinations were negative for tubercle bacilli. During this time the patient lost weight but the physical findings remain unchanged. Additional examinations revealed a mononucleosis, negative skin reactions to tuberculin (Moro and intracutaneous). Guinea pig inoculations with sputum gave negative results. None of the animals died from tuberculosis but on examination of sections there were found several times epithelioid infiltrations and sometimes pus with scarce acid-fast bacilli. Cultures of the pus gave at first negative results but, after twenty days' growth on potato medium, a colony grew having the morphological characteristics of the human tubercle bacillus. The patient had plaques of lupus pernio on the face. Biopsy revealed Boeck's sarcoidosis. Histological examination of an axillary lymph node showed hyperplasia with granulomata composed of pure epithelioid cells without giant cells. Radiological examination of the fingers and toes revealed *ostitis cystica*. It was now possible to diagnose the condition as Boeck's sarcoidosis involving the skin, lung, bones and lymph nodes. The patient died in March, 1938 with progressive dyspnoea caused by cardiac insufficiency.

Autopsy revealed reddish plaques in the skin. The lungs were reduced in size. On section, the right lung was occupied by a diffuse sclerotic process without evidence of

tuberculosis. The remainder of the parenchyma had a gelatinous appearance. The left lung showed a finer sclerosis in the apical and subapical regions.

The histological appearance was that of an exudative-degenerative endoalveolitis. Only in one field were there numerous giant cells but without caseation. The epitrochlear lymph nodes contained numerous epithelioid cells but no giant cells and no caseation. In the liver a few isolated epithelioid granulomata were found. The other organs showed nothing remarkable. The lymph nodes of the mediastinum were replaced by fibrous tissue. (The description hardly justifies the diagnosis of sarcoidosis.)

(14) *Froehlich and Scherer:* The report concerns a woman of fifty who developed increasing weakness, loss of appetite and vague abdominal complaints for about a year prior to her admission to the hospital. Later she noted a swelling in the region of the spleen. Examination revealed marked dyspnoea, tachycardia and a left pleural effusion. The liver and spleen were enlarged. Pleural puncture revealed a haemorrhagic effusion which contained numerous lymphocytes and erythrocytes. Culture and guinea pig inoculation did not yield tubercle bacilli. Splenic puncture revealed a high percentage of monocytes and nests of endothelial cells. Sternal puncture revealed an increase in monocytes. Roentgen examination of the chest showed a density in the left thorax with displacement of the mediastinum to the right. The right hilar lymph nodes were enlarged. In the right lung there were numerous small nodules. It was quite difficult to diagnose the condition, Hodgkin's disease being considered a strong possibility. The patient died in heart failure.

On postmortem examination, no tuberculosis was found in any of the lesions. The spleen weighed 1,027 g., the capsule was somewhat thickened with adhesions at the upper pole. On cut-surface, the tissue was gray-red and replaced by tissue consisting of very small nodules and strings. Similar foci were present in the liver. The lymph nodes (deep cervical, paratracheal, hilar, peripancreatic, periduodenal and portal) were huge, composed of separate, single nodes with whitish thickened capsule.

Microscopical examination revealed all the lesions to be of the type of an infectious granuloma similar to tuberculosis. The youngest lesions were in the tonsils and tracheal mucosa, the oldest and most extensive ones in the lungs, spleen, mediastinal and abdominal lymph nodes. No lesions were present in the heart, kidneys, pancreas, ovaries and bone marrow. No acid-fast bacilli were found in sections. The description is that of sarcoidosis but none of the microphotographs presented are very typical.

(15) *Berg:* A man of thirty-six gave a history of osseous tuberculosis in a brother. During infancy he was well. In 1936 he contracted an inflammation of the parotid glands, associated with fever which persisted for about a month. A week after he had recovered, he developed iritis of both eyes. He was treated in a hospital for four months. An X-ray film of the chest at this time revealed increased hilar shadows on both sides. Later films showed in addition to the hilar densities small infiltrations in both lungs. Repeated examinations of the sputum failed to reveal tubercle bacilli. The Pirquet and Wassermann reactions were negative. On subsequent occasions he reacted faintly to intracutaneous tuberculin (0.01 mg.). The final diagnosis was pulmonary tuberculosis and tuberculous iritis. In 1938, he was transferred to another sanatorium. His condition was good except for slight dyspnoea. Physical examination was essentially negative. An X-ray film of the chest showed increase in the infiltrations in both lungs which were confluent in places. The pupils were small, irregular and showed synechiae. Another intracutaneous tuberculin test was negative to 0.1, 1 and 3 mg. Additional examinations

of the sputum and gastric contents failed to reveal tubercle bacilli. In time he began to lose weight, have slight fever, develop vertigo and hallucinations. At other times, he was excited and mentally disordered. He died with the temperature showing a steep rise.

Autopsy: The only findings were fine, palpable, nodulations throughout the upper portions of the lungs and a marked increase of peribronchial and perivascular connective tissue. The nodulations consisted of small, gray tubercles which were widely scattered through the pulmonary tissue and which showed histologically typical sarcoid structure. The peribronchial and perivascular lesions were designated as *lymphangitis fibrosa*. In these connective tissue strands, many epithelioid tubercles with giant cells were seen. Some of them showed central necrosis. No granulomatous lesions were found in any other organ. Tubercle bacilli could not be demonstrated in sections of the pulmonary tubercles. No bacteriological work was done on the postmortem material.

Bergstrand, who did the histological work, stresses the point that he could find only in one tubercle the inclusion bodies that he seems to consider pathognomonic for sarcoidosis and that he is, therefore, not entirely convinced of the diagnosis, sarcoidosis. However, he doubts very much that the patient had tuberculosis.

(16) *Voldet:* The first patient, a man of fifty-six, stated that his mother had died from tuberculosis. His illness began five years previously with cough and abundant expectoration. Tubercle bacilli were not found in the sputum. Repeated inoculations into guinea pigs also proved negative. Increasing dyspnoea and cyanosis were soon associated with right heart failure and cachexia which caused death.

The pertinent findings at autopsy were as follows: bilateral pleural fibrosis; anthracotic pulmonary fibrosis, particularly marked in the apices; disseminated nodular lesions throughout the lower lobes, mainly along bronchi and blood vessels; these were up to 8 mm. in diameter and showed no caseation; diffuse bilateral emphysema and marked anthracosis of the hilar lymph nodes. There were no abnormal findings in any of the other organs.

Histological study showed in the lungs an endarteritis in which process giant cells were prominent. There was obliterative bronchiolitis. In the pulmonary parenchyma minute accumulations of epithelioid cells were seen. The dilated alveoli contained heart-failure cells, some fibrin and oedema fluid and there was vascular engorgement. (The accompanying microphotographs show lesions suggestive of sarcoidosis but they contain many giant cells giving an appearance that is commonly seen in strictly productive tuberculous foci.)

(17) *Voldet:* The second patient, a man of forty-nine gave a history of dyspnoea and cyanosis of the face and extremities for a period of eight years. He had cough and expectoration, lost weight but had no fever. At no time did he have haemoptysis. A few months before death, he developed an acute febrile episode which was diagnosed as bronchopneumonia. The sputum did not reveal acid-fast organisms. He died with signs of cardiac insufficiency.

The autopsy revealed an empyema in the left pleural cavity; granulomata scattered throughout both lungs; peribronchial and perivascular nodular fibrosis; massive sclerosis of hilar lymph nodes; fibrous foci in the Malpighian bodies in the spleen.

Histological examination showed that the granulomata consisted of epithelioid and giant cells. The peribronchial and perivascular fibrous tissue contained some cholesterol deposits. No tubercle bacilli could be demonstrated in sections nor by animal inoculation.

(18) *Tice and Sweany:* The patient was a forty-five year old woman whose chief complaints were cough and dyspnoea. Physical examination revealed nothing remarkable. There were no cervical or axillary lymph nodes and no splenic enlargement. Six sputum examinations were negative for tubercle bacilli. X-ray films of the chest revealed mediastinal shadows, more prominent on the right and irregular infiltrations in both lung fields. A diagnosis of Hodgkin's disease was made and she received roentgen-ray therapy. Later films of the chest revealed an increase in the hilar mass and greater involvement of the right upper lobe. The diagnoses considered, were: pulmonary tuberculosis, Hodgkin's disease, Ayerza's disease and mediastinal tumor. She died with symptoms of increasing dyspnoea.

Autopsy was performed by Dr. R. Yale Lyman. The organs were sent to Doctor Kirschbaum for diagnosis. Sections and lung tissue were studied by the authors. The pleural and pericardial cavities contained straw-colored fluid. The heart was considerably hypertrophied. No significant changes were found at autopsy, excepting in the lungs and hilar lymph nodes. The left lung weighed 675 g. The pleura was shiny, moist and mottled with grayish areas. The right superior lobe was markedly contracted. There was a nodular, firm, middle lobe, contracted and fibrotic. Along the mediastinal borders of the right lower lobe were several blebs. There was crepitation of the lower lobe. The upper lobes were firm and noncrepitant. There was a cavity 2 x 1 x 1 cm., surrounded by a fibrotic capsule.

Sections of the lung parenchyma revealed small plaques of fibrous tissue that were not densely hyalinized with occasional giant cells. Many of the small arteries were completely obliterated by endarteritis. There were no lesions other than those of the lungs and hilar lymph nodes. No acid-fast bacilli were ever found and no caseation was present anywhere in the postmortem material.

(19) *King:* The writer describes the roentgenographic features of sarcoidosis from a study of 50 cases. He includes a brief description of one case examined at autopsy. In 1919, the patient had a splenectomy and a spleen weighing 58 ounces was removed. Review of the microscopical slides in 1939 established the diagnosis of sarcoidosis. In 1920, the roentgenogram showed "spots in the lung" which by 1924 had increased in size. At this time, the patient began to cough, expectorate and developed pleural pain. The symptoms lasted for fifteen years, until death. Repeated films of the chest revealed coarse mottling at first and later dense infiltration with cavities in both apices. At autopsy, Dr. Reuben Schulz found sarcoid lesions in the lungs, lymph nodes and liver.

(20) *Hollister and Harrell:* A nineteen year old Negro experienced for a period of four years progressive, painless enlargement of the lymph nodes first in the inguinal regions and later in the cervical, submental, axillary, epitrochlear, postauricular and occipital regions. He developed cough and expectoration, lost weight, had chest pain and fever. He noted skin lesions and later felt pain in the terminal phalanges of the fingers and toes. X-ray film of the chest revealed "snow-flake-like densities evenly distributed throughout both lungs most marked in the right apex." Cultures for fungi and inoculations of sputum into guinea pigs gave negative results. The skin reaction to 1 mg. of Old Tuberculin was negative; later it was 2 plus to a dilution of 1:10,000. Examination revealed numerous discrete rounded, painless, papular lesions on the extensor surfaces of the arms and legs and on the buttocks. All the lymph nodes were enlarged. The tonsils were large and red. A few dry inspiratory râles were heard in the mid-lung fields posteriorly. Another X-ray examination of the chest showed no change. X-ray films of the fingers and toes

showed numerous punched-out areas in the phalanges. On the ninth day in the hospital, tonsillectomy was done. The temperature rose sharply at first and fell on the fourth day. The patient appeared stronger but he suddenly became comatose and died.

Autopsy revealed Boeck's sarcoidosis, involving the skin, lymph nodes (generalized), lungs, liver, spleen, kidneys, peritoneal surfaces of the diaphragm and stomach, tonsils, epiglottis, bone marrow of vertebrae, ribs and phalanges of toes, and phalangeal synovial membrane. The subpleural regions of both lungs were studded with irregular, slightly elevated, pale green plaques, measuring 1 to 3 mm. in size. On section, the parenchyma was firm, indurated, pinkish-gray and studded with firm, shot-like nodules. The interlobar septa and the walls of the bronchi showed extensive scar-like thickening which decreased the size of the lumina of the bronchi. Microscopical examination revealed discrete and confluent collections of noncaseating epithelioid tubercles disseminated throughout both lungs. The denser areas of epithelioid proliferation were present where normally a greater condensation of lymphoid tissue and a larger number of lymphatic channels existed. The larger collections, made up of dense fibrous connective tissue and fibro-epithelioid tubercles, were found around the hilum. The walls of many blood vessels were thickened and occasionally the lumen was almost completely obliterated by a hyaline mass. Dense collections of fibro-epithelioid tubercles surrounded the bronchi, causing mural thickening and partial or complete compression of the lumina. The sarcoid lesions in all involved organs consisted of a collection of discrete and confluent tubercles. Some of the tubercles consisted of collections of epithelioid cells; others were made up of homogeneous fibrous tissue. In the liver and spleen, the tubercles contained central caseous areas, surrounded by concentric zones of epithelioid cells and outer dense zones of lymphocytes.

Tubercle bacilli were recovered in guinea pigs inoculated with material from a lymph node from the hilum of the liver. None were recovered from animals inoculated with material from other organs, spinal fluid and blood.

The authors conclude that the patient may have had two diseases: localized tuberculosis, from which organisms were recovered, and sarcoidosis, the aetiological agent of which remains unidentified.

(21) *Kraus:* An instance of sarcoidosis is described in a woman, aged forty-one, who had also an endocrine disease, characterized by dystrophia, cessation of menses, hypotrichosis and polyuria. The endocrine disturbance was found to be caused by a granuloma involving the infundibulum, the pituitary stalk and the pituitary gland itself. Death was caused by thrombocytopenia which was not referable to the sarcoidosis or to the endocrine disturbance.

Autopsy revealed old tuberculosis of the pulmonary apices with fibrous adhesive pleuritis; circumscribed bronchiectasis of the left lung and peculiar granulomata in all lobes of the lungs and all internal lymph nodes and spleen; chronic splenic tumor; cirrhosis of the liver; chronic cholecystitis and cholelithiasis; osteoporosis; haemorrhage in the nasal cavity; ecchymoses in serous membranes; anaemia. The granulomata, as seen in the lungs, appeared as tiny grayish nodules closely compacted; in the left lower lobe a fine network of scar tissue was found in some places. Cultures on Löwenstein's medium taken from various organs for tubercle bacilli were sterile after six weeks' observation. Guinea pigs, rabbits and chickens inoculated with the same tissues did not show any lesions after fifty-seven days. Guinea pigs inoculated with tissues of the above-mentioned animals showed no pathological changes after fifty-three days.

Microscopically the granulomata were tiny nodules, made up of epithelioid cells,

lymphocytes and giant cells differing from those of tuberculosis. The nodules showed a tendency to be surrounded by a thin hyaline capsule; there was no induration and no caseation. They contained peculiar inclusions, consisting of an apparently organic base impregnated by calcium and iron salts, while other inclusions seemed to be cholesterol crystals. The inclusions gave rise to foreign body giant cells, but some of the latter did not seem to be related to the inclusions. The histological appearance was considered characteristic of sarcoidosis.

(22) *Zollinger and v. Meyenburg:* An instance is cited of a twenty-one year old man who died of an atypical and unusually rapid multiple sclerosis. There were found in the brain wide-spread granulomata which consisted of epithelioid cells, giant cells, largely of the Langhans type, and a peripheral border of lymphocytes. Although of tuberculoid structure, caseation was absent and microörganisms were not demonstrable. Granulomata of similar appearance were found also in the paratracheal lymph nodes which were considerably enlarged. A calcified primary tuberculous focus was also found. Since other causes could be excluded, the tuberculous aetiology of the granulomata seemed most likely. The opinion is advanced that the condition was an instance of atypical Boeck's disease, similar to that described by others. The authors favor the tuberculous origin of Boeck's disease.

(23) Among the discussors of the foregoing case, *Scheidegger* cites an instance of an acutely progressive Boeck's sarcoidosis with granulomata in the meninges. Animal inoculation with material from various organs were negative for tubercle bacilli.

(24) *Uehlinger* relates the case of a soldier who also had cerebral localizations. Histologically there was present sclerosing, epithelioid cell granulation tissue.

(25) *Nicod* describes a case of granulomatosis localized exclusively in the ependyma, possibly analogous to Meyenburg's case.

DISCUSSION

One of the problematical points in the pathogenesis of sarcoidosis is tuberculin anergy. Of the 26 autopsied cases presented here, 14 were tested with tuberculin. Definite reactions were obtained in 5 (cases 3, 5, 10, 20 and 26). Of these, case 3 showed typical and only noncaseating lesions at autopsy; but in this patient a tuberculin reaction could be elicited only after tuberculin treatment; cases 5, 20 and 26 showed some caseating lesions on necropsy and, in the latter two, tubercle bacilli were demonstrated; case 10, too, showed necrotic lesions, but whether or not this patient really had sarcoidosis remains uncertain on the basis of the published findings.

However, to state that 5 cases had a tuberculin reaction does not imply that the remaining 21 cases were anergic. This can be stated only for 5 cases (2, 4, 8, 11 and 15), because the remainder either were not tested at all or with insufficient doses. It is disappointing to find that the actual frequency of tuberculin anergy in proved cases of sarcoidosis is still to be determined.

The diagnostic histological criteria of sarcoidosis are well established. However, the more autopsy reports are published, the more it is realized that some caseation not infrequently occurs and that it cannot be accepted as a criterion

against the diagnosis of sarcoidosis. Out of the 26 cases, some caseous or necrotic foci or centres were reported in 8 (cases 1, 4, 5, 10, 12, 15, 20 and 26). Whether this is explained as one of the possible developments of sarcoidosis *per se* or as a secondary infection with tubercle bacilli depends entirely on the observers' aetiological conviction.

Inclusion bodies within giant cells or within hyaline tissues are described in 4 cases (cases 1, 15, 21 and 26). They stain like calcific material and, at times, like elastic fibres. They seem to be more frequent in the lung than in other organs and may be remnants of elastic fibres which have been destroyed by the granulomatous tissue and have become incrusted with calcium salts. That they have any aetiological significance or that they are pathognomonic for sarcoidosis appears most unlikely.

The present series of cases does not seem to add anything essential to the solution of the aetiological question. It is obvious that it is extremely rare to find tubercle bacilli in sarcoidosis and, when they do occur, they are so scarce that they are, as a rule, demonstrable only by animal inoculation. Hence it is impossible to learn anything definite of the topographic relation between bacilli and cells. Demonstrable caseation, as mentioned, is not rare; and tubercle bacilli have repeatedly been demonstrated in such caseated lesions. If they are demonstrated by animal inoculation from cases in which caseation is not reported (case 9), the existence of some minute caseous lesions cannot be excluded with certainty. In our case, tubercle bacilli were easily found in sections through caseated lesions, but never in those through noncaseated foci. If demonstration of tubercle bacilli were the necessary condition for the diagnosis of tuberculosis, about 80 per cent of all primary foci in adults could not be so diagnosed.

Without repeating the discussion on the aetiology of sarcoidosis presented in a previous paper (26), it would appear that the failure of demonstrating tubercle bacilli in the majority of sarcoid lesions is not a convincing argument against their tuberculous aetiology, nor is the occasional presence of tubercle bacilli in sarcoid lesions, mostly in those with *some* caseous elements, a positive proof.

Attention was directed to the occurrence of so-called anticutins in the serum of sarcoid patients. In only one of the 26 cases was the presence of anticutins attempted and verified (case 3). Pinner, Weiss and Cohen (28) have reported studies on anticutins and procutins in normal, tuberculous and sarcoid persons. In 4 of 11 sarcoid patients anticutins were present and in 4 other ones, procutins. But anticutins were also demonstrated in small percentages of normals (3 to 9 per cent) and in various groups of tuberculous patients (up to 18 per cent). The highest percentage of anticutins was found in the serum of 23 tuberculous patients with low allergy. We do not believe that anticutins play a significant immunological rôle in sarcoidosis; their occurrence is neither diagnostic nor pathognomonic.

To round out this report it may be of interest to mention some of the outstanding clinical features of sarcoidosis which were observed in the present series of autopsied cases. The disease was found in 13 males and 8 females; in 5 the sex was not mentioned. This ratio, however, does not represent the true

incidence of the disease in the two sexes; the majority of reported clinical observations have been in females. The youngest patient in our series was an infant of three months (case 8); the oldest, a woman of sixty-eight years (case 3). According to Leitner (29), the disease has been reported in an infant as young as three weeks and in an individual of seventy. The majority of patients with sarcoidosis are adults between twenty and forty years. The occasional presence of sarcoidosis in members of the same family has aroused some speculation as to possible constitutional factors in the disease. Five authors have reported the disease in sisters (29). Case 12 of this series is such an instance. The histories of some of the autopsied cases contained sufficient information to allow an estimation of the duration of the disease. The infant of three months (case 8) lived six weeks; case 1 lived for seventeen years; the majority lived for periods ranging from three to eight years.

Noteworthy about the clinical aspects of sarcoidosis is the fact that a number of syndromes are morphologically related and can be grouped under the same disease (26). The 26 autopsied cases include one or more of such diverse syndromes as uveoparotid fever or Heerfordt's disease (cases 15 and *M. de F.*); Boeck's sarcoid of the skin (cases 2, 3, 7, 8, 10, 11, 12, 13, 20 and *M. de F.*); *ostitis multiplex cystoides* or Jüngling's disease (cases 2, 4, 13 and 20); benign lymphogranulomatosis or Schaumann's disease (cases 4, 5, 8, 13, 15 and 18); torpid and atypical forms of disseminated tuberculosis (cases 1 and 9); localizations in the pituitary gland (cases 21 and *M. de F.*) and in other organs such as the brain, calvarium, adrenals, heart and diaphragm which gave rise to bizarre clinical manifestations.

SUMMARY

The clinical and pathological findings in 43 autopsied cases, diagnosed as sarcoidosis, are collected from the literature. One case, observed by the authors, is added.

SUMARIO

De la literatura se han recopilado los hallazgos clínicos y patológicos en 43 autopsias de casos diagnosticados como sarcoidosis. Agrégase además un caso observado por los A.A.

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TUBERCULOSIS IN EMPLOYED WOMEN

Morbidity and Mortality Trends in Relation to Age

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During the past forty years remarkable strides have been made in the curbing of tuberculosis mortality. Morbidity also has declined continuously since the beginning of the century. Presumably, morbidity and mortality among women in industry also have decreased since the death rate for all females has diminished, while an increasing number of women have entered industry.[2] However, the dearth of statistics on both morbidity and mortality among women by occupations forces the writer to rely largely upon conclusions drawn by experts in this field.

From discussions by doctors, public health officials and other research workers in tuberculosis, especially those presented in the Saranac Symposium, it is clear that women are subject to special hazards in such fields as nursing, medical schools, hospital laboratory work, in such employment as waitresses, saleswomen and conductors, and in trades that may expose them to inhalation of injurious dusts (11). This apparently is due to the fact that they are either in close and constant contact with cases of tuberculosis, enter it unknowingly in the passing stream of tuberculosis, or inhale dusts which presumably predispose the lungs to infection by the tubercle bacillus.

In order to try to gauge the extent of death attributed to tuberculosis among working women, we must rely largely upon studies made for relatively limited groups of people, upon deductions from other statistics and upon observations made by experts in the field, since no authoritative statistics have been compiled. Investigations have been made by health associations and other organizations to try to determine the causes underlying deaths due to tuberculosis among women. These studies have included a determination of the marital and industrial status of the women concerned and so throw some light on this matter. The Metropolitan Life Insurance Company also has prepared data showing the decline in mortality among its women policyholders.

Recently attention has been called repeatedly to the very large number of young women, nurses, medical students, laboratory technicians, etc., who have become infected. Special studies have been made of these groups and considerable factual data published. However, fully comparable data for employed women generally are lacking, so it is difficult to draw deductions concerning mortality and morbidity in nurses relative to women in industry. Almost the only statistics showing morbidity among women are those which have been prepared by the U. S. Public Health Service from reports of industrial sick

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[2] Recent indications, since this paper was written, point to a reversal, at least temporarily, in this trend, owing to war-time exigencies. Longer working periods, relaxed selectivity policies and reduced medical attention due to diversion of doctors and nurses to the armed services are among the contributing factors.

benefit organizations on disabling morbidity (7). These statistics appear to indicate that tuberculosis frequency declined steadily from 1932 to 1940. However, these data have a number of inherent limitations, especially since membership is limited to certain occupations and ages. Further, the diminution in

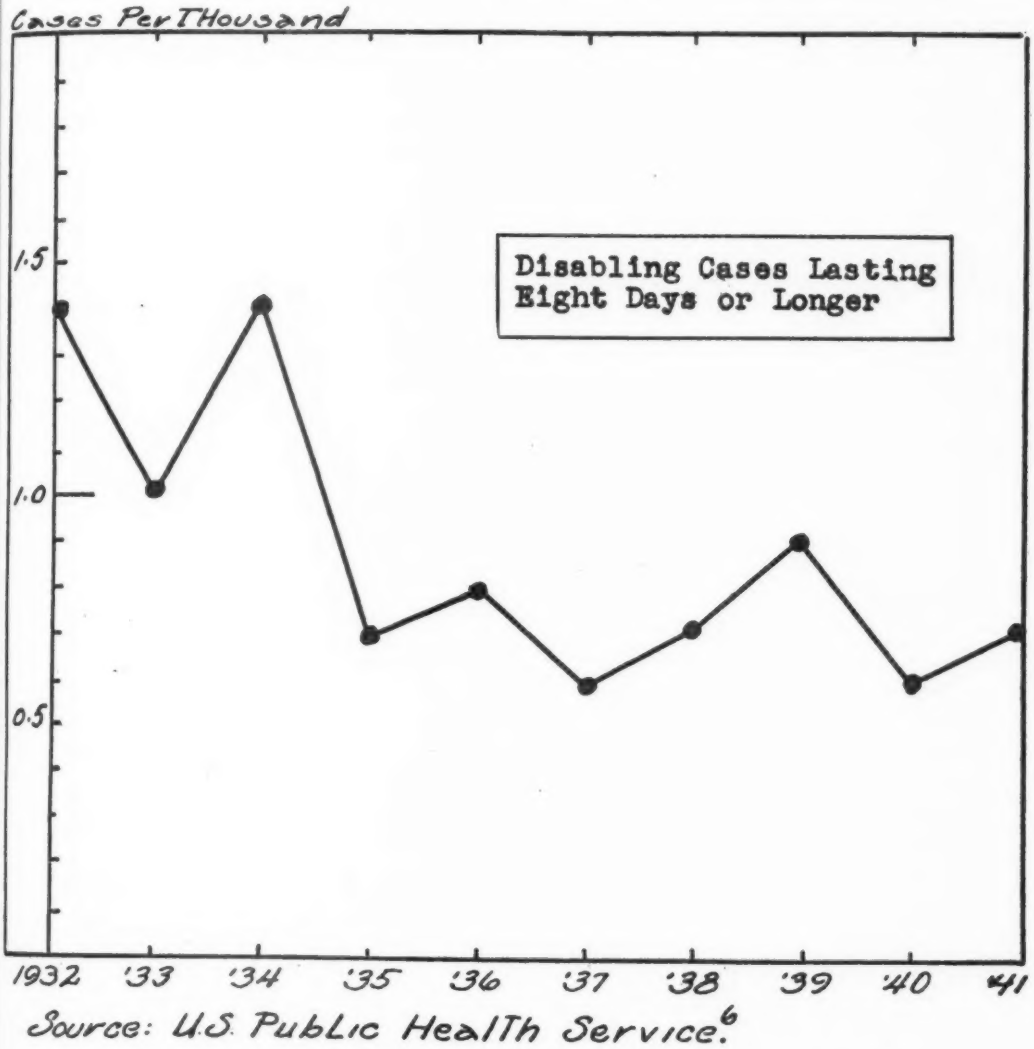

CHART 1. Tuberculosis morbidity among female employees in various industries

tuberculosis frequency may have been influenced by improvement in economic conditions as the country recovered from the depression in the early thirties. (See chart 1.)

Tuberculosis mortality among both men and women has declined continuously during the past four decades. A special study carried in Mortality Statistics,

1911, (13) shows that remarkable progress was made within the ten-year period, 1901–1911, mortality for all ages of both sexes falling 17 per cent. The female death rate declined more than the male even in the age groups fifteen to nineteen, twenty to twenty-four and twenty-five to twenty-nine, although deaths per 100,000 continued considerably higher than in the same male age groups.

Census data show that mortality from tuberculosis has diminished since 1911 both among males and females. However, the decline among certain female age groups in recent years has lagged behind male experience.

In 1901 the total deaths in the age group fifteen to twenty-four were 425.3 for females and 365.4 per 100,000 for males, or roughly in the case of the former, some 16.5 per cent higher. But in 1940 female deaths in that group were 58 per cent larger, indicating that progress in checking of tuberculosis deaths among females has been less than in the case of males.

On the other hand, mortality among these age groups declined from 1901 to 1911, so that the failure of female deaths in the fifteen to twenty-four age groups to decline commensurately with male experience in the past three decades has led some to assume that the growing employment of women may have

TABLE 1

*Deaths in registration states from all forms of tuberculosis per 100,000 population**

	TOTAL POPULATION		
	All	Male	Female
1920	113.1	116.6	109.5
1930	71.1	76.2	65.9
1940	45.9	54.2	37.5

* U. S. Bureau of Census (14).

been the prime contributing factor in this lower achievement in the control of tuberculosis ravages (3).

Statistics compiled by the Metropolitan Life Insurance Company for death rates per 100,000 among white males and females by age periods in the years 1911–1915 and 1935–1939 show a similar trend (4). However, these data show a remarkable decline in female deaths notwithstanding the fact that mortality among young adult women has not decreased as greatly as among the same ages in male groups.

Deaths per 100,000 of population in the registration area were 194.4 in 1900, 153.8 in 1910 (14), and thereafter have continued to decline, as shown in table 1. The white female death experience clearly has been more favorable than the male, as far as all age groups and all women are concerned.

It will be noted from chart 2 that the drop in mortality for the critical age groups, that is, fifteen to nineteen and twenty to twenty-four, has been almost as great as for women as a whole. In fact, in the fifteen to nineteen group the drop was greater than for any other group. It would be highly dangerous to generalize from such a small and selective sample, but this experience does

tend to provide some basis for wondering whether the entry of women into industry on a wider scale has retarded progress in checking tuberculosis mortal-

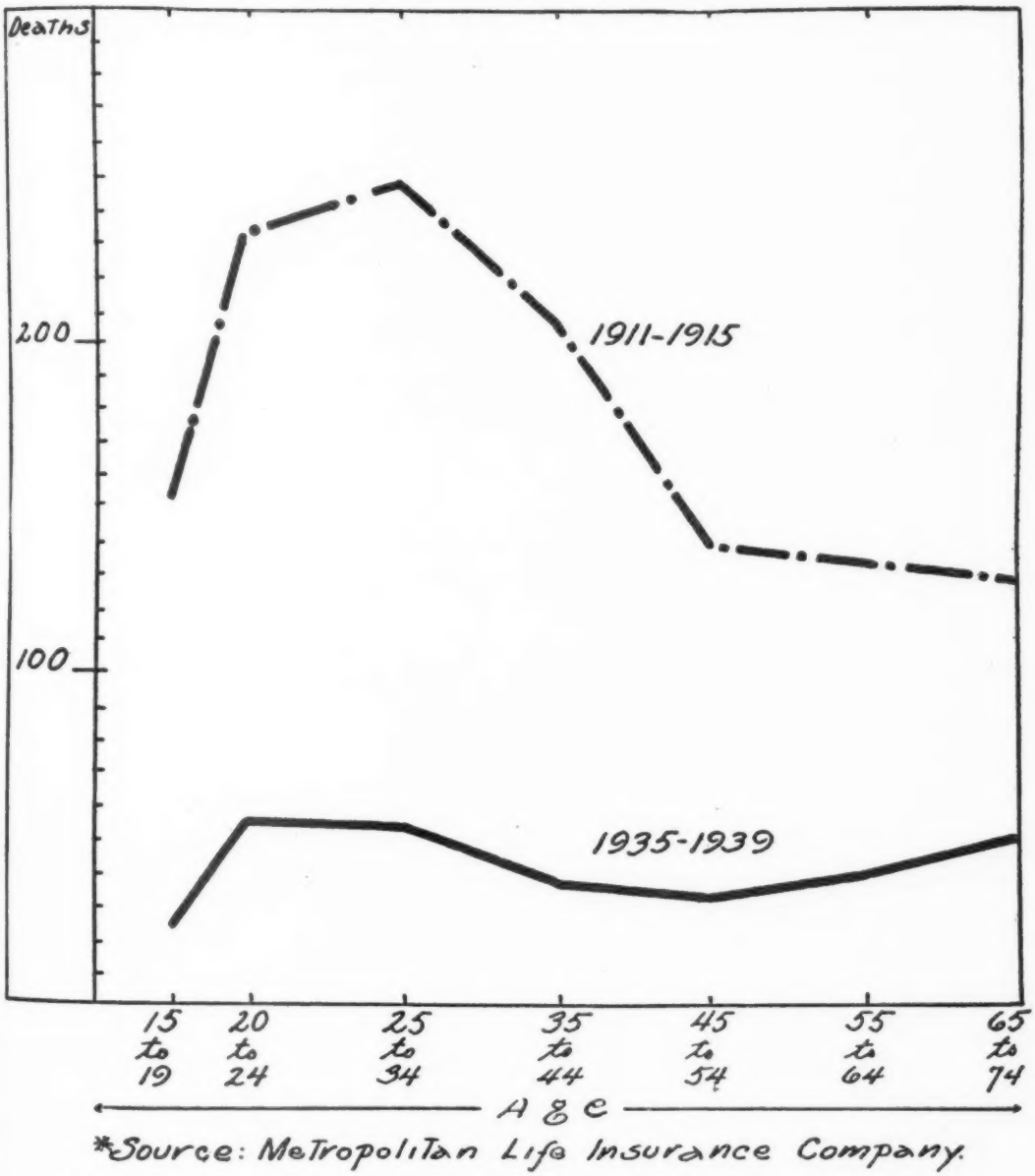

CHART 2. Average death rates per 100,000 policyholders (white females) by age groups

ity. The inference from these statistics, it would seem, would be to the contrary since a large number of working women are numbered among the policyholders.

Of course, it may also be that, since the women in question are of the higher paid wage-earning class generally, the economic status factor again is a major determining element.

In summarizing conclusions to be drawn from these two studies (10, 15) by the National Tuberculosis Association of deaths due to tuberculosis among young women generally and among nurses, Nicholson states that industrialization cannot be considered as being responsible for high tuberculosis mortality. She declares further that there is no reasonable basis for thinking that such factors as modern clothes, dieting, poor food habits, too little sleep or unusual recreational habits have been responsible either. Nicholson believes that, even though it cannot be proved statistically, the physical changes of adolescence and early adult life cause young women to be especially susceptible to tuberculosis and these are the chief reasons for high death rates. Nicholson also thinks that early marriage and childbearing may tend to increase the death rate among young women.

In support of this inference, Nicholson states that New York City, with fewer girls over fifteen married, has a lower tuberculosis death rate than the country as a whole, and Detroit with more girls married has a higher rate. A causal relationship between these facts has not been proved yet, Nicholson concludes, but she considers that the occurrence may be significant.

The authors of *Tuberculosis among Nurses* state that tuberculin tests in colleges and among other adult groups (12) have shown that a steadily declining proportion of the population becomes infected with tuberculosis during childhood and adolescence.

One comparison of student nurses in Bellevue Hospital and of female employees of the Metropolitan Life Insurance Company shows an incidence of 0.68 per year for the nurses and 0.25 for women policyholders aged eighteen to twenty-two (1). A study of 11,100 female college students in New York City, cited in *Tuberculosis among Nurses*, found 3.6 per 1,000 were tuberculous and only 2.1 per 1,000 clinically significant (5, 2). Still another study among nurses in four New York training schools showed an annual incidence of 6.7 per 1,000.

Mariette's study (9) of patients at the Glen Lake Sanatorium led him to conclude that tuberculosis among nurses is discovered much earlier than among the general population, which gives nurses a far better chance for recovery. The death incidence among nurses who were patients was 11.6 per cent as compared with 40 per cent for women patients generally.

The statistics and studies cited earlier and the Saranac Symposium provide only inferential information, in the main, on morbidity among employed women, with the notable exception of nurses and college students and employees of insurance companies. The mortality data are, except for women as a whole, limited to special studies since no large, comprehensive surveys have been devoted to study of tuberculosis deaths among employed women as differentiated from other women. Such a study of itself would present great problems even if funds were available for the work.

A large proportion of employed women also do housework to a varying degree, probably have children and assume household responsibilities. Further, it has been estimated that fully 85 per cent of employed persons are hired by small concerns who do not have health services. The large concerns with health services would not provide a truly representative picture as many of them do not hire tuberculous persons and also weed out the tuberculous promptly. Most women do not work in a given occupation over a period of years as men do. So one must rely largely on end-evidence of morbidity, that is, mortality, among women generally, and upon observations made by those working in the field.

The failure of deaths from tuberculosis among women in the age group twenty to twenty-four and those groups immediately above and below this to decline during the past forty years commensurately with the drop in young male mortality has led to the conclusion that the changed status of women may have accounted at least in part for this. All authorities agree that physiological factors play a predominant rôle in the high morbidity and mortality in young adult females. However, it also has been pointed out that the suceptibility of young women has been aggravated by such modern trends as slimming diets, late hours, wider use by women of alcohol and tobacco, and by the industrial competition between men and women. This deduction, as pointed out before, is challenged by others, notably by Nicholson (10).

With such diametrically opposed views concerning the high incidence of tuberculosis among young adult women, the writer obviously can draw no categorical conclusions as to whether, aside from certain dangerous occupations, the incidence is higher among employed young women than it is among other women aged fifteen to twenty-five or thereabouts. However, there seems to be much evidence to support the opinion that, except for the hazardous occupations (where young women are in close and constant contact with tuberculosis), the economic status of the workers rather than employment in industry or professions is the major factor in tuberculosis mortality and very probably also in tuberculosis morbidity among women aged fifteen to twenty-five.

The study of tuberculosis mortality made by the British Registrar General (8) seems to bear out the conclusion that economic status is the major factor in tuberculosis mortality, aside from some especially hazardous occupations.

This report is based on 1930–1932 census data and lists death rates according to social classes. Table 2 shows standard mortality rates for men in each class and also for their wives.

It will be noted that the death rate rises from the professional class to the unskilled workers both for the men and their wives. And, what is particularly noteworthy, the rate for the wives is lower in the group with the highest economic status than for the husbands, but higher than the males in group V, where wages are lowest. The mortality of the wives, who have little or no industrial exposure, apparently also varies by socio-economic class in the same way (4).

This study also contains interesting information concerning single women.

It was found that deaths of single women from tuberculosis, as disclosed by death registers, compared fairly well with the number revealed by the 1930–1932 census. Accordingly, a study was undertaken to see if such varied as to economic status as male mortality did. Also, findings for single women are compared with deaths among married women, classified as to their husband's occupation.

The death rate for single women in the semi-skilled group is slightly lower than for married women for ages twenty to twenty-five. This is also true for unskilled workers, while for those women falling between the skilled and unskilled classes, the death rate was higher than for married women. However, the variation is not striking and it would seem to bear out the assumption that, barring those occupations in which a special hazard exists, mortality among young employed women probably is not significantly greater than among women generally of the same age groups. This seems to indicate that socio-economic status *per se* is a more important factor than occupation in determining tuberculosis morbidity and mortality among women in the majority of occupations

TABLE 2

*Respiratory tuberculosis standardized mortality ratios for ages twenty to sixty-five—England and Wales—1930–1932**

CLASS	STANDARDIZED MORTALITY RATIOS	
	Males	Married women
All classes	100	100
Professional, etc.—I	61	52
Semi-skilled, etc.—II	70	67
Skilled—III	100	99
Intermediate—IV	104	106
Unskilled—V	125	132

* Great Britain Registrar General (8).

and that probably physiological factors account largely for the failure of the mortality in the fifteen to twenty-five group in this country to fall as sharply during the past few decades as the death rates among the same male age groups.

Other factors may become increasingly important in the immediate future under the stress of war-time conditions. Longer working hours, the possibility of increasing strain and worry over the outcome of the war and those directly involved may prove predisposing factors to tuberculous infection. Health programs may be allowed to lapse somewhat owing to the shortage of doctors and nurses and to other factors. This also may lead to reduced detection of tuberculosis among workers, facilitating the spread of infection. Overcrowding in homes or factories or both also may add to the hazard. Thus, less effective health programs, which generally stress detection and segregation of tuberculous individuals, and overcrowding in homes and factories may increase morbidity because of the greater exposure to the tubercle bacillus.

Relatively high family income no longer will assure families of those amenities

to which they have been accustomed. In fact, the standard of living may decline, even though "real" income continues to expand, thus tending to retard the generally successful compaign against tuberculosis.

SUMMARY

Economic status is the major determining factor in mortality and morbidity from tuberculosis among young employed women. Less favorable progress during the past forty years in curbing the incidence of tuberculosis among young women as compared with young men apparently is not due primarily to the increasing employment of women in industry. Occupational risk is evident where women, especially in the twenty to twenty-five year age group, are in in close and constant contact with tuberculosis or subject to "dust" hazards. However, tuberculosis mortality among young employed women, with such notable exceptions, probably is not significantly greater than among women generally of the same age groups and similar economic status.

SUMARIO

La situación económica es el principal factor determinante en la mortalidad y morbidad tuberculosas entre las jóvenes empleadas. El adelanto menos favorable obtenido durante los últimos cuarenta años en la lucha contra la tuberculosis en las jóvenes comparado con los jóvenes, al parecer no se debe primordialmente al creciente empleo de las mujeres en la industria. Resulta manifiesto el riesgo profesional cuando las mujeres, en particular las de 20 a 25 años de edad, se encuentran en íntimo y constante contacto con la tuberculosis o se hallan expuestas al peligro del "polvo". Sin embargo, la mortalidad tuberculosa entre las jóvenes empleadas, aparte de esas notables excepciones, probablemente no es mucho mayor que en las mujeres que pertenecen en general a los mismos grupos de edades y tienen una situación económica semejante.

ACKNOWLEDGMENT

In order to bring data up to date with actual experience, much of which has not as yet made its way into medical literature, it was thought wise to interview workers in tuberculosis research, especially as applied to the field of Industrial Medicine.

Interviews were obtained therefore with Dr. Leverett D. Bristol, Health Director, American Telephone and Telegraph Company; Dr. May Mayer, Division of Industrial Health, New York Department; statisticians at the Metropolitan Life Insurance Company, the National Tuberculosis Association and the New York Tuberculosis and Health Association, all of whom proved very helpful. However, all expressed an opinion that comprehensive statistics in this field are sadly lacking.

Acknowledgment is hereby made of this valuable assistance.

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EFFECT OF YEAST UPON THE TOXIC REACTIONS OF PROMIN ON TUBERCULOUS GUINEA PIGS[1]

GEORGE M. HIGGINS AND WILLIAM H. FELDMAN

Although recent reports have described the influence which diets may have upon the toxicity of drugs, it is of interest to recall that more than twenty years ago Funk (1) expressed the opinion that diets may exert significant changes in the toxic reactions induced by drugs.

With the recent advent of the sulfonamide compounds to clinical use the influence of diets and of certain vitamins upon their toxicity has been experimentally tested. Para-aminobenzoic acid has been shown to antagonize the effect of sulfanilamide (2). Liver extract and para-aminobenzoic acid were found to antagonize the effect that sulfaguanidine induced upon the growth of rats (3). The curative action of nicotinic acid in black tongue of dogs was nullified by sulfapyridine, but whole liver restored the therapeutic value of the vitamin (4, 5). High protein diets were found to impede the bacteriostatic action of certain sulfonamide compounds (6) and to afford considerable protection to rats which were given large amounts of sulfanilamide (7). Total liver extract in doses of 100 mg. per kilogram diminished the deaths due to large amounts of sulfanilamide from 50 to 25 per cent (8). Liver and yeast, when added in concentrations of 1 to 2 per cent to purified diets, afforded protection against the damage induced by succinylsulfathiazole (9).

Previous observations have shown that certain drugs belonging to the sulfone series of compounds exert a striking inhibitory effect upon experimental tuberculous infections within a relatively short period of treatment. One of us (W. H. F.) has found that compounds such as sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate (promin), disodium formaldehyde sulfoxylate diaminodiphenylsulfone and 4,4′-diaminodiphenylsulfone are each capable after sixty days' administration, perorally, of accomplishing a demonstrable deterrent effect upon the development of the disease in experimentally infected guinea pigs.

Certain toxic effects, however, are invariably induced in guinea pigs, (10, 11) and in all mammals, as far as known, which receive these drugs. The erythrocytes appear to be most susceptible to damage and a form of anaemia resembling the haemolytic type occurs. There are marked macrocytosis, a reduction of the haemoglobin level and an elevated percentage of reticulocytes.

In a study of such toxic effects induced in rats by the oral administration of promin, one of us (G. M. H.) learned (12) that certain fractions of the B vitamin appeared to provide some protection against the tendencies of the drug toward destruction of blood. When rats fed purified diets, especially those containing low protein but high carbohydrate levels, are given promin daily, there develops within ten days to two weeks a definite syndrome, including transient loss of weight, varying degrees of alopecia and marked hypochromic

[1] From the Division of Experimental Medicine, Mayo Foundation, Rochester, Minnesota.

anaemia. When animals were fed such diets and permitted to select freely the water-soluble B vitamins, from convenient bottles attached to their cage, this characteristic promin syndrome was considerably mitigated. There was no loss of weight, no loss of hair and the blood levels were more nearly normal. Furthermore, a subsequent study has shown that when animals were fed these purified diets to which were added other foods known to be rich in vitamin B, such as yeast or liver, promin failed to induce the characteristic toxic reactions which occurred when rats ate the unsupplemented purified diet. With these preliminary observations on rats in mind, we projected a study to test the effect of feeding our regular ration,[2] to which a high percentage of yeast was added, upon tuberculous guinea pigs receiving promin. We wished to know whether these toxic changes which occur in the blood stream could be mitigated somewhat by yeast and whether the addition of this food constituent to the regular ration would in any way modify the deterrent or therapeutic values of promin in experimentally infected tuberculous animals.

EXPERIMENTAL METHODS

Five groups of guinea pigs consisting of 6 animals each were selected. All were adult males whose average weight was approximately 0.5 kg. The animals were caged in pairs. The distinguishing features of each of the five groups were as follows: group 1, infected and fed the regular laboratory ration only; group 2, infected and fed the regular ration to which was added brewers' yeast, strain K, in amounts equal to 13 per cent by weight; group 3, infected and fed the regular ration to which was added promin to the amount of 1 per cent by weight; group 4, infected and fed the regular ration containing, in addition, 13 per cent of yeast by weight and 1 per cent of promin by weight; group 5, not infected and fed the regular laboratory ration to which was added 13 per cent by weight of yeast.

After the animals had been eating their respective rations for five days, each guinea pig was inoculated subcutaneously, in the sternal region, with 0.1 mg. of a thirteen-day-old culture of virulent human tubercle bacilli (H37rv). The experiment was terminated sixty days later.

On the last day of the experiment, 3 cc. of blood were taken from the heart of each animal and thoroughly oxalated; 2 cc. were used to determine the concentration in milligrams per 100 cc. of blood of the promin[3] and 1 cc. was used for the routine haematological examination. The latter consisted of making a total erythrocyte and leucocyte count; the determination, by the use of the haematocrit, of the volume in cubic micra of the erythrocytes; the grams of haemoglobin per 100 cc. of blood; the differential distribution of the leucocytes; and the percentage of reticulocytes of the total number of erythrocytes. Material for subsequent histological examination was preserved from the lungs, liver, spleen, the site of inoculation and the regional lymph nodes of each animal.

[2] The regular laboratory ration consisted of so-called Rabbit Chow which was supplemented with fresh leafy vegetables twice weekly.

[3] The determination of promin in the blood was done by Dr. Osterberg and his associates of the Section on Clinical Biochemistry.

In addition approximately a half of each spleen was suspended and cultured for tubercle bacilli.

RESULTS

All animals were living when the experiment was terminated. Considering the relatively short time that the infection had been present this was not unexpected.

Since the object of the experiment was principally to ascertain whether or not yeast would inactivate the promin or otherwise interfere with the capacity of this sulfone derivative to cope successfully with a tuberculous infection, the tuberculous changes present in the tissues of predilection were observed microscopically and the results of this portion of the study were recorded numerically.

The scheme (13) followed for recording the pathological changes is based on the arbitrary selection of 100 as the theoretic maximal number of units of tuberculosis possible in any one animal. The character of the disease—whether progressive or nonprogressive—and the extent of the involvement of the various organs are the factors of importance in determining the number of units of infection.

Although the number of animals in each group was small, the differences in the average indices of infection between groups 1 and 2, which did not receive the sulfone compound, and groups 3 and 4, which did, were striking and indicate clearly the favorable influence of promin either alone or in combination with yeast. These distinctions become even more impressive if one considers in each group the tuberculosis in the lungs, liver and spleen only, disregarding the tissues in the regions where the infection was introduced. Considered in this manner, the indices for the respective groups (based on a maximum of 90 units) were: group 1, controls, 50.9; group 2, yeast, 43.1; group 3, promin, 2.9; and group 4, promin and yeast, 2.7.

Concentration of promin in the blood: There was no essential difference of concentration of promin in the blood between the animals that received promin only and those that received promin plus the yeast. The average concentration in mg. per 100 cc. for the animals that received promin was 8.9 (6.5–12.4)[4] while for the animals that received both the promin and the yeast the average concentration was 9.5 (8.2–10.3) mg. per 100 cc.

Splenic cultures: Of the 6 spleens cultured from the control group (group 1), acid-fast bacilli were obtained from 5. The same results were obtained from the spleens of the animals that received yeast only. Of the 6 spleens from the group that received promin but no yeast, positive results were obtained from 3, while from the spleens from the animals in the group that received promin and yeast positive results were obtained in only one. The results of the attempts to culture tubercle bacilli from the spleens of the 24 animals may be summarized as follows: Of the 12 animals that did not receive promin the results were positive in 10. Of the 12 animals that did receive promin (or promin and yeast) the results were positive in only 4.

Haematological data: The haematological data pertaining to the erythrocytes

[4] Numbers in parentheses are ranges.

and the haemoglobin levels are set forth in table 1. Since no significant changes in the total number of leucocytes nor in their differential distributions were observed in any of the five groups, these data have not been included in table 1.

The addition of yeast to the regular ration (group 5) was without effect upon the blood constituents observed. Tuberculous guinea pigs which ate the regular ration (group 1) or the regular ration to which yeast had been added (group 2) had erythrocyte levels, erythrocyte volumes, haemoglobin concentrations and reticulocyte percentages statistically alike and comparable to those observed in nontuberculous guinea pigs.

Guinea pigs which received the regular ration and promin (group 3) were anaemic. Their erythrocyte and haemoglobin levels were significantly lower than their controls, while their erythrocyte volumes and reticulocyte percentages were significantly higher. The addition of the yeast complement to the diet of animals receiving promin (group 4) did not significantly improve the blood

TABLE 1

Effect of promin, of brewers' yeast or of both on the erythrocytes of guinea pigs

GROUP	ANIMALS	ERYTHROCYTES PER CU. MM.	ERYTHROCYTE VOLUME	HAEMOGLOBIN	RETICULOCYTES
			cu. micra	*g. per 100 cc.*	*per cent*
1—Infected, regular ration	6	5.7 ± 0.1	87.7 ± 2.1	14.2 ± 0.9	1.2 ± 0.01
2—Infected, regular ration plus brewers' yeast	6	5.5 ± 0.2	88.3 ± 2.4	13.4 ± 0.3	1.8 ± 0.03
3—Infected, regular ration plus promin	6	3.9 ± 0.2	119.5 ± 4.5	12.6 ± 0.2	9.5 ± 0.6
4—Infected, regular ration plus promin and brewers' yeast	6	4.4 ± 0.1	105.3 ± 2.6	12.7 ± 0.3	11.9 ± 0.6
5—Not infected, controls, regular ration plus brewers' yeast	6	5.5 ± 0.4	93.5 ± 1.4	14.3 ± 0.4	1.8 ± 0.01

picture. Although the average erythrocyte count was higher than in those receiving promin but not yeast, the difference between the two (0.5 ± 0.2) is not adequate to enable one to conclude that the yeast was of any value. Although the average cell volume in this group (105.3 ± 2.6 cubic micra) is considerably less than in group 3, a fact consistent with the higher erythrocyte count in group 4, the difference between the two is only 14.2 ± 5.2 and we must again conclude that the addition of yeast was inadequate to prevent the usual toxic effects that promin induced upon the erythrocytes.

COMMENT

The results obtained from this study of the effect of yeast upon the changes exerted by promin upon the erythrocytes of guinea pigs are not of the order anticipated from the preliminary study on rats (12). Although yeast, when added to a purified high carbohydrate diet, did not abolish the toxic effects upon

the erythrocytes of rats given promin, significant improvements were observed, not only in the total number of erythrocytes but in their size and in haemoglobin levels as well. The guinea pigs used in the present study were, of course, tuberculous and the efficiency of yeast in counteracting the effect of promin may have been modified. We do not know the effect which yeast may have upon normal prominized guinea pigs. The rat has been the animal of choice in studying the rôle of diets and foods rich in vitamins upon the toxicity of chemical compounds and it may be that the guinea pig is unsuitable for studies of this sort. Except for the reactions in the blood stream, guinea pigs appear to withstand the effects of the drug better than rats. We have observed guinea pigs which have received promin in an amount equal to 1 per cent by weight in their diets for one year and yet we have never seen untoward effects grossly. We have never seen a loss of weight in guinea pigs as we have in rats. There is no loss of hair and, with the doses used, hyperexcitability has not been observed. The hypochromic anaemia, however, is common to both guinea pigs and rats given promin.

Although the yeast did not significantly alter the extent of anaemia induced by the drug in these tuberculous guinea pigs, it likewise did not impede the deterrent or therapeutic value of promin upon the course of the disease. Using the numerical index (13) devised to record the extent of tuberculous infection in guinea pigs, we obtained values which were essentially alike in animals which had received promin and those which had received promin plus the yeast. Thus, whatever the action of promin may be, yeast did not influence its action adversely.

The data assembled from cultures of the spleens indicate the possibility that the addition of yeast to the promin may have had value. Only one positive culture was obtained from the spleens of this group, while 3 were obtained from the group which received promin alone and 5 were obtained from the control group. The number of animals in each group is, of course, too small to enable one to conclude that significant results accrued as a result of the yeast component in the diet.

SUMMARY AND CONCLUSIONS

On the principle that whole liver, liver extracts, yeast and such foods high in vitamin B content, when given to white rats, have been found to minimize the toxic symptoms of the sulfonamide compounds as well as the sulfone, promin, we have studied the result of adding a high component of brewers' yeast (strain K) to the diet of tuberculous guinea pigs receiving promin.

Our conclusions are:

1. The addition of yeast to the diet of tuberculous guinea pigs receiving promin did not significantly improve the moderate blood dyscrasia which the drug induced.

2. Brewers' yeast (strain K) added to the diet of tuberculous guinea pigs receiving promin did not modify in any way the expected therapeutic efficacy of the drug.

3. The importance of the sulfone series of compounds in combating experimental tuberculosis would seem to warrant further studies of this sort, directed toward the possible rôle of nutritional factors in precluding or alleviating the toxic effects of the drug.

SUMARIO Y CONCLUSIONES

Partiendo del principio de que el hígado íntegro, los extractos hepáticos, la levadura y alimentos semejantes ricos en vitamina B, cuando se suministran a las ratas blancas, aminoran los síntomas tóxicos de los sulfamidados así como de la sulfona, promina, estúdiase el resultado obtenido al agregar un alto componente de levadura de cerveza (cepa K) a la dieta de los cobayos tuberculosos que recibían promina, llegándose a estas conclusiones:

1. La adición de levadura a la dieta de los cobayos tuberculosos que recibían promina, no mejoró mayor cosa la hemodiscrasia provocada por la droga.

2. La levadura de cerveza (cepa K) agregada a la dieta de los cobayos tuberculosos que recibían promina, no modificó en modo alguna la eficacia terapéutica que se esperaba de la droga.

3. La importancia de la serie de compuestos de la sulfona para combatir la tuberculosis experimental, parece justificar estudios ulteriores del mismo género, encaminados a determinar el posible papel de los factores nutritivos en evitar o aliviar los efectos tóxicos de la droga.

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BOOKS

H. A. PATTISON: *Rehabilitation of the Tuberculous. Pp. 186, The Livingston Press, Livingston, Columbia County, New York, 1942, fabrikoid, $2.50.*

By LOUIS E. SILTZBACH

This readable little book aptly addresses the layman as well as the physician. Both will find it pertinent, especially now when manpower shortages accent the need for information about the work capacities and work adjustments of the tuberculous.

The thesis that recovering tuberculous patients require a transition period of graduated, purposive effort before resuming every-day activities is to-day universally accepted. Yet we have scant knowledge of this aspect of recovery and few projects for applying what facts we possess. For seventeen years, however, the author of this book has directed a successful rehabilitation scheme: The Potts Memorial Institute, Inc. He draws on that experience to show how the patient is to be guided through the postmedical period when mishap and misstep often combine to rob him of the benefits he has gained from treatment.

Two main points are constantly stressed throughout the text. The first is that, if recurrences are to be kept down to a minimum level, the patient must not be discharged from treatment until stability of the lesion has been achieved. For, without such stability, all subsequent effort devoted to his rehabilitation will avail little. The second point is that the patient must further be brought to a status at which he is medically, socio-economically and psychologically equipped to handle his postsanatorium environment. This can be accomplished, the author shows, only if the patient is approached on an individual, highly personalized basis, preferably while he is still at the sanatorium.

Chapters on medical treatment in the rehabilitation centre, and on clinical criteria for establishing the eligibility and suitability of patients for undertaking work training or schooling are particularly informative. These are illuminated by representative case histories which signal the direction in which the physician and his coworkers will find the solution of many complex problems.

A concluding section is devoted to brief sketches of some typical rehabilitation projects throughout the world. The author describes several well developed in-sanatorium programs emphasizing their importance in getting the patient prepared for the rehabilitation centre, or for vocational training and work in industry. More extensively treated are the special centres which include not only Potts Memorial Institute but also Altro Work Shops and Boston Sheltered Shop in this country; and abroad, Papworth Village, Preston Hall and Bilthoven among others.

These successful projects, the author observes, are able to serve but a small proportion of the patients who could profit from such facilities. He also discusses briefly the unbalanced state of our tripartite program to conquer the disease: early diagnosis, adequate treatment and rehabilitation—and shows that

only treatment has been executed on a wide scale. His discussion calls to mind the statement of the late Sir Pendrill Varrier-Jones, founder of Papworth Village: "Our present attack is all middle and no ends. . . ." To-day this statement would have to be amended, for, since the war began, there has occurred a spectacular improvement at one "end" of the program. As readers of the July, 1943 issue of the REVIEW may recall, it is estimated that by the end of 1943 about 14 million adults in this country will have had a chest roentgenogram in connection with induction into the armed forces and into war industry. Thus, we are really beginning to get "early diagnosis" on a mass scale. But, in spite of some increase in interest, there has been no such progress at the rehabilitation "end." There, as the author demonstrates, the pace is still a limp. Indeed, as long ago as April, 1913, the eminent Dr. Hermann M. Biggs clearly recognized the importance of sound rehabilitation schemes and he persuaded both branches of the New York State legislature to authorize special workshops for the tuberculous. They were not carried through and relatively little has been accomplished in the field since.

Constantly concerned with the human side of his subject, Doctor Pattison dwells upon the importance of handling the recovering patient as a living and aspiring person. He portrays amusingly his bewilderment when he is called upon to decide whether or not any of the 17,452 jobs listed in a government occupations manual is suitable for a specific patient. Would the calling elephant keeper be suitable? He wondered about that for many years until one day, while visiting a farm, he came upon three elephants who were being wintered there. After watching the laborious procedures of feeding, bedding down and the toilette including a manicure, he definitely struck this occupation from his list.

The book is well put together and clearly printed—a concrete sample of the competence of properly managed patients at the rehabilitation centre whose product it is.

DOROTHY STOPFORD PRICE: *Tuberculosis in Childhood. With a chapter on Tuberculous Orthopaedic Lesions and other contributions by Henry F. MacAuley. Pp. vii + 215, with 87 illustrations, Bristol: John Wright & Sons Ltd., London: Simpkin Marshall Ltd., 1942, fabrikoid.*

By CAMILLE KERESZTURI COYLEY

From war-torn England has come to us a small book, on poor quality paper, written by Dorothy Price. However, in contrast with the quality of paper, is the richness and the conciseness of the material. Dorothy Price gives the impression that she has personal experience in all phases of tuberculosis in children. Still she is modest and quotes other leading phthisiologists liberally. Almost every statement which is made in her book is solidly substantiated by facts and figures and an excellent up-to-date bibliography. The book is clearly written and combines the virtues of a textbook and a handbook. It contains 215 small octavo pages and can be carried in one's pocket with great ease. It is a helpful

book for the medical student, the graduate doctor and, because of its excellent bibliography, also for the research worker in tuberculosis. The only poor part of the book is the chapter on orthopedics which was written by Henry F. MacAuley. This chapter is elementary, incomplete and old fashioned. It gives the point of view of Henry MacAuley and not of the majority of the orthopedists of our time.

There are only a few statements in the book which can be challenged. They are as follows: (*1*) Page 21, "Primary skin tuberculosis does not take place through an already existing skin lesion in children." Most of the carefully observed and published cases of the literature seem to have a nonspecific skin defect preceding the appearance of the typical primary focus of the skin. (*2*) Page 30, "Lung tissue infections respond to a weaker dilution of tuberculin than do abdominal or cervical glands." The experience of most of us who observed many thousands of tuberculin reactions seem to indicate the reverse trend of tuberculin sensitivity. (*3*) Page 30, "Primary tuberculous infection occurs at some time in the life history of every individual." This statement was true in the past for some of the European countries, but it is certainly not true any more, especially in the U. S. A. (*4*) Page 31, "In children under three years a positive tuberculin test points to active disease. Even in 50 per cent of positive cases under 14 years the disease is not completely healed and treatment or supervision is required." Most of us clinicians would consider this statement far too conservative. A child with a positive tuberculin test but without signs and symptoms of clinical disease and a normal erythrocyte sedimentation rate is considered by most of us inactive and does not need any treatment. (*5*) Page 35, "Calcification is uncommon in infants because the degree of caseation which would lead to visible calcification often proves fatal." When one X-rays routinely every tuberculin-positive infant one often is amazed how frequently and in what a short time calcification can appear in tuberculous infants and children. (*6*) Page 36, Dorothy Price has more faith in the "treatment" of tuberculosis than we have. She says, "miliary tuberculosis is very common in untreated infants." We feel that miliary tuberculosis depends on the massivity of infection, the virulence of the tubercle bacilli, the resistance of the patient and not on the treatment proper. In other words, we appreciate the rôle of chance in the outcome of tuberculosis more than the rôle of our treatment. (*7*) Page 62, "In the 4–14 year age period, cough is present in 50 per cent of cases suffering from primary tuberculosis." This figure seems to be much higher than our experience would indicate. (*8*) Page 79, "Hair line lying along the direction of the interlobar septum thickening towards the hilum indicates old pleurisy." American X-ray men specializing in children seem to think that visible interlobar line is a normal phenomenon if rapid exposures are used and the child occupies a certain position when the picture is taken. (*9*) Page 87, "Miliary tuberculosis is rarely seen in countries where all children from tuberculous homes are examined and treated early." Page 137, "If all pulmonary cases were diagnosed during primary infection and treatment instituted there would be complete cure in very nearly 100 per cent of the cases." Unfortunately this statement is not correct and miliary

tuberculosis is still an unpredictable accident of infected children in spite of early diagnosis and therapy. (*10*) Page 150, "In tuberculous phlyctens the skin test will always be positive though two strengths up to 1:100 Mantoux may have to be used." Our experience is that patients with tuberculous phlyctenular conjunctivitis are usually violently allergic and give a positive skin reaction sometimes even to 1:1,000,000 OT and always to 1:10,000 dilution. (*11*) Page 150, "Hospitalization of patients 1–4 years of age with phlyctenular keratoconjunctivitis is essential for an early cure." In the U. S. A. we hospitalize tuberculous children less frequently than in Europe and especially rarely for phlyctenulosis. (*12*) Page 150, "The child with chronic corneal phlyctenular disease has very poor vision, cannot attend school and grows up with few prospects of earning a livelihood." Chronic phlyctenulosis in the U. S. A. is extremely rare and leads very seldom to more than slight impairment of vision. (*13*) Page 159, "Danger of dissemination arises only on rare occasions in cervical adenitis and mainly after operative interference." We never saw any postoperative dissemination in our more than 100 cases of cervical adenitis operated on at Babies Hospital, New York. (*14*) Page 159, "The onset of tuberculous adenitis is gradual and comparatively painless." We are observing more and more tuberculous cervical adenitis, the onset of which is so acute that the histological finding of tuberculosis is a complete surprise. (*15*) Page 160, "The chest radiogram is negative if the cervical glands are primarily infected." This statement is not correct in the majority of cases. There is a vast number of patients with tuberculosis of cervical lymph nodes in whom the chest roentgenogram is negative, still the cervical adenitis is not due to primary tuberculous infection. (*16*) Page 164, "The conservative treatment of tuberculous cervical adenitis is beyond question superior to operative treatment from the cosmetic point of view." This statement would be true if one could be sure that no conservatively treated patient suffered spontaneous breaking down and fistula formation of his lymph nodes.

In general, Dorothy Price believes more in the physician's power of preventing tuberculosis deaths in children than we do. She overrates the value of therapy and is much more emphatic about the length and intensity of sanatorium care, rest and the administration of roborants than we in the U. S. A. are. About ten to fifteen years ago the management of tuberculous children was similar in this country to what it is now in England. In recent years we came to the realization that rest, hospitalization, drugs and climate play a far lesser rôle in the outcome of tuberculosis among children. On the other hand, we became more emphatic about breaking up tuberculosis contact with the adult source case and about applying surgery to suitable cases in form of pneumothorax, thoracoplasty and various fusion operations.

There were two very significant statements made in Dorothy Price's book which are especially meaningful because they come from England. On page 118 she says, "In recent years it has been accepted as proved that young people exposed to infection are less prone to develop pulmonary tuberculosis if they possess a positive tuberculin reaction and a satisfactorily healed childhood primary focus." On page 140 we find: "There is one outstanding prophylactic meas-

ure which has passed from the phase of experiment to the stage of established fact; that is BCG vaccination, notably as carried out in the City of Gothenburg in Sweden." Some of us who watched the English phthisiologists come to this conclusion in the course of almost twenty years appreciate the statement of Dorothy Price on this subject. As a whole, *Tuberculosis in Childhood* is a first-rate book, the best of its kind. Every medical student and physician interested in tuberculosis ought to read it.

Conference on Tuberculosis Isolation. Sponsored by the California State Department of Public Health. Held at Los Angeles, March 20, 1943. Pp. iv + 86, with appendices of 12 pp., mimeographed, paper.

By EMIL BOGEN

The isolation of communicable cases of tuberculosis is an important part of the control program. The forcible isolation of the recalcitrant cases has not yet been widely adopted. In Los Angeles County, however, under the leadership of the late Dr. J. L. Pomeroy, Health Officer, and Dr. P. K. Telford, Chief of the Division of Tuberculosis, a policy of enforced isolation whenever indicated has been followed for more than a dozen years. More recently other health departments have adopted a similar program.

Because of the success of the program in Los Angeles County and because of the need for a careful study of the problem by all interested parties, Dr. Edward Kupka, Chief of the Bureau of Tuberculosis of the California Department of Public Health, arranged a meeting of health officers, tuberculosis control officers, sanatorium superintendents, representatives of the California Attorney General's Office and others, at the State Building in Los Angeles on March 20, 1943. This conference constitutes a milestone in the progress of tuberculosis control. Its proceedings were published in mimeographed form, and were also abstracted freely in California's Health, the monthly bulletin of the State Department of Public Health, for August 31, 1943, volume 1, number 4, pages 21 to 24 inclusive. They should be of great interest to all concerned in the control of tuberculosis.

There was general agreement that the statutes in effect at the present time are sufficient to provide proper legal backing. The chief barrier to a more active program seemed to be a general lack of appreciation of its importance and necessity. Once this has been made clear, health officers, district attorneys and judges feel less hesitancy in compelling the isolation of the recalcitrant tuberculous in suitable institutions or other locations where protection will be assured. More than a score of discussants brought out the various difficulties which face the health officer in carrying out such isolation, and pointed out how they might be overcome.

The extensive experience of Los Angeles County was first described by Doctor Telford and then the problems of other counties were discussed by their physicians, both health officers and sanatorium directors. Considerable discussion was devoted to standards of communicability, and the inadvisability of relying

unduly upon individual casual negative reports, especially when inconsistent with clinical findings, was stressed. The legal phases of the problem were discussed authoritatively by Mr. A. M. Martin, Deputy Attorney General of California, with extensive references to the laws and judicial decisions, both in California and elsewhere, under which such action may be taken.

The general conclusions of the conference were as follows:

1. The local health officer is authorized to quarantine or isolate a person with communicable tuberculosis; he may do this without consultation with or direction from the State Health Department.

2. The local health officer must be prudent in the selection of suitable cases for coercive action; he must be able to show that reasonable cause exists.

3. Enforced isolation is to be resorted to only after thorough trial of persuasion and explanation has been made.

4. A person who breaks tuberculosis isolation is guilty of a misdemeanor, for which he can and should be prosecuted.

5. Recalcitrant tuberculous frequently present complicating factors, such as chronic alcoholism or border-line psychosis.

6. The experience in Los Angeles County has shown the practicability of enforced isolation of the tuberculous.

7. A campaign of education on the occasional necessity of enforced isolation of the tuberculous is in order.

JAMES R. LISA AND MILTON B. ROSENBLATT: *Bronchiectasis. Pp. x + 190, with 40 illustrations, Oxford University Press, London, New York, Toronto, 1943, fabrikoid.*

By WILLIAM E. ANSPACH

Many articles on bronchiectasis have appeared in the past decade. Opinions expressed have been diversified and often appeared contradictory. A major article has seemed to be ripe for some time, one based upon a broad experience, leading to correct evaluation of all of the evidence presented on this subject. The authors have tackled the job by a generous allotment of space to the work of others. References are made to 220 articles, in the 173 pages of the text. The method most frequently employed is one of stating the opinion of various authors and then the authors show their preference or give their opinion. Only occasionally, they have left the reader to make the decisions and only infrequently must one look elsewhere in the book to discover the authors' stand. I have found this newest book on bronchiectasis delightfully easy to read.

For convenience, the author's cases (110) were divided into two groups: Group I, primary (9 cases), "primary" meaning that the major pathological changes in the lung were those of bronchiectasis. Group II consisted of cases in which bronchiectasis was secondary or an incidental finding (101 cases).

Pathological findings on a primary group of 9 are presented in the form of tables. One case was two months of age and was thought to classify as of con-

genital origin. The ages of the remainder ranged from forty-three to seventy-six years. The majority gave a history of the presence of previous pulmonary disease and had productive cough and dyspnoea for a period of from ten to twenty-five years. In the main, gross pathological changes were indicative of chronic inflammatory disease of the lung. The parenchyma showed marked fibrosis, the walls of the ectatic bronchi were usually thick and fibrous, the mucosa presented a granular appearance, in some the bronchi were thin. The exudate in the bronchial lumina was usually purulent and often contained thick necrotic material. In one instance it was foul smelling. The basement membrane was preserved. The muscle layer showed hypertrophy and moderate fibrous tissue replacement. The elastic fibres were thickened but relatively unimpaired. Plasma cell infiltration of the bronchial wall was extensive and lymphoid infiltration moderate. The blood vessels were unaffected, the parenchyma showed marked interstitial fibrosis. Adjacent bronchi were normal or emphysematous. Gram-positive cocci were found in the bronchial wall and in the exudate.

In group II, in which bronchiectasis was not the dominant lesion, the pathological changes were essentially those of group I. In 50 cases, bronchiectasis was associated with bronchopneumonia, 19 with tuberculosis, 11 with lobar pneumonia, 7 with a primary or metastatic carcinoma. Other conditions were lung abscess, pneumonoconiosis and heart disease. Ages and details of individual cases in this group are not given.

Many illustrations of the first changes in the bronchi are included. The photomicrographs have been carefully selected, well reproduced and constitute a graphic argument that early changes in the bronchi and bronchioles are destructive in nature. The authors rationalize that these changes, which they have found, followed infections and lead directly to bronchiectasis.

A brief discussion of the anatomy and physiology of the lung is presented. Emphasis is placed upon the destructive nature of infection which causes bronchial dilatation. It is presented as a disease affecting all portions of the lung, not merely the bronchi. The dilated bronchus is looked upon as a cavity. The authors believe that the destructive process is predominant and do not feel that mechanical factors are necessary or play an important rôle. Atelectasis is recognized as a common associated finding, but it is not considered to play a significant part in the pathological process.

Under clinical aspects of bronchiectasis, discussing aetiology, the authors state that "while there are many anatomic pathways for infections to travel from the sinuses to the lower respiratory tract, the concept of sinusitis as a cause of bronchiectasis, does not fit, either with clinical or pathological experience. Sinusitis is a very common disease in the general population and its incidence bears no relationship to that of bronchiectasis. The pathological changes in bronchiectasis are those of pulmonary necrosis in association with severe pneumonitis... There is no proof that sinusitis can cause bronchiectasis directly or indirectly."

"Observations of cases of idiopathic chronic bronchitis for a period of fifteen years revealed no development of apparent bronchiectasis except following intercurrent pneumonia."

It is significant that studies of bronchiectasis which are limited to children show a very small percentage of cases without a history of previous infection, while studies of older groups show a large percentage with negative past history. "The only possible explanation . . . is that the pneumonic infection antedated the onset of bronchiectatic symptoms by many years and was therefore forgotten."

"Bronchiectasis which is of clinical importance develops in those cases in which the bronchopneumonic infection is associated with extensive bronchopulmonary destruction, comparable to the type of destruction observed in cases of foreign body aspiration and putrid lung abscess. It is an irreparable disease due to the fibrous tissue replacement of the destroyed bronchopulmonary tissue."

"The maximum result that can be achieved with all forms of palliative therapy is symptomatic improvement. However, the patient still retains the infected pulmonary tissue and recurrent exacerbations are not prevented. Removal of the involved area offers the only possibility for complete eradication of the disease. The chances of succumbing to the operation are far less than the chances of succumbing to the disease within two decades after the onset. Preoperative failure to recognize the disease of the lingula . . . has resulted in the continuation of the symptoms despite the successful removal of the left lower lobe." Resection of the lingula was necessary in 80 per cent of the cases of Churchill and Belsey, according to the authors.

A one paragraph summary seems to cover the high spots of the broader discussions covered earlier in the book and gives a clue to the authors' opinions. It is as follows:

"Bronchiectasis is a disease of the bronchi and the associated pulmonary parenchyma. It is not merely a dilatation of the bronchial tubes. The pathological changes consist of inflammation of the bronchial walls and the adjacent parenchyma. They include all degrees of changes from mild polynuclear reaction to complete necrosis. The end stage is one of fibrous replacement of the destroyed elements. The epithelium is the only tissue that regenerates. The so-called bronchial dilatation is actually an epithelialized cavity communicating with a bronchus. The etiology of the disease is bacterial infection. The pathological changes are similar regardless of the infecting organism. The vast majority of cases are sequelae of bronchopneumonia in childhood. Bronchiectasis may also be produced by influenza, tuberculosis, putrid lung abscess, fungus disease and other pulmonary infections. In cases of bronchiectasis due to bronchial tumor, extrinsic bronchial pressure, or foreign body aspiration, the etiological factor is the infection which results from the bronchial occlusion. The clinical course of bronchiectasis and the prognosis are based upon the degree of pulmonary infection. The size of the dilated cavities, *per se*, is of no clinical importance. Spontaneous cure is rare and the disease is characterized by recurring exacerbations of the pulmonary infection, with eventual fatal termination. The only definitive treatment is surgical resection of the involved pulmonary tissue."

In the above summary the word atelectasis is not mentioned and bronchial

occlusion is mentioned only in connection with bronchial tumors, extrinsic bronchial pressure or foreign bodies. It seems to me, if the authors had had a wider experience with clinical bronchiectasis in infants and children (they mention only one child in their group) to which they attribute the vast majority of cases, they would not minimize atelectasis as a diagnostic sign or thick secretions as an obstructive medium. From a pathological point of view, obstruction merely aids infection by inhibiting drainage which in turn accentuates the destructive process, as nicely set out by the authors, but the clinical signs of atelectasis, both physical and roentgenological, offer a clue to the presence of a process in which obstruction is present and eventually will lead to bronchiectasis if air patency is not reëstablished. The "definite treatment" of bronchiectasis is surgical resection, according to the authors. Postural drainage and bronchial aspiration are apparently for palliative treatment, not for prophylactic treatment.

The authors do not seem to be ready to recognize persistent atelectasis as indicating a process which is a precursor of bronchiectasis during which bronchoscopic aspiration and postural drainage offer an opportunity to prevent permanent damage. This recognition of the prebronchiectatic stage is of the greatest importance in young children. A low surgical mortality in lobectomy is no excuse for overlooking the disease process in its initial stage when a high percentage of bronchiectasis can be prevented. Besides, lobectomy or pneumonectomy offer no cure to cases of bilateral involvement and the mortality on a whole is actually near 50 per cent, not less than 4 per cent as reported by a few outstanding surgeons and quoted by the authors.

In the text, the authors quote Weinberg, who introduced sandburs into the bronchi of rabbits, and Adams *et al.*, who used 35 per cent silver nitrate and thermal cautery to produce bronchial stenosis. The former concluded that bronchiectasis followed complete obstruction. The latter found bronchiectasis only in bronchi that were patent. The authors conclude that "obviously, if one group of experiments leads to the conclusion that complete bronchial obstruction is essential and another group demonstrates the reverse, it is not illogical to assume that bronchial obstruction, whether partial or complete, is not the basic factor in the production of bronchiectasis." After a restudy of these two articles, I fail to see any discrepancy or statements that are necessarily contradictory. Complete occlusion of the bronchus is necessary for atelectasis. Both experimenters found atelectasis to be present in abundance. When ectasia occurs, better drainage is afforded, indicating that the lumina have enlarged; the obstruction has diminished in size, or the secretions have become less viscid. This accounts for the presence of air commonly seen in the saccules and the patency of the bronchi in the advanced areas.

Mechanical factors in infants and children seem to play a significant diagnostic rôle roentgenologically and should not be passed up in a complete discussion of treatment. The authors' "primary group" contained reference to only one child and it was thought to fulfill the requirements of the *rare* congenital, not the *common* acquired form of bronchiectasis.

The authors attribute the majority of cases to bronchopneumonia but do not

emphasize the signs of detection of this "pneumonia" which is often very different from the usual form. Bronchial stenosis is so regularly present in young children in this disease process that the associated atelectasis is more diagnostic than it is in bronchogenic carcinoma in adults. The chances of complete recovery by bronchoscopic aspiration and postural drainage, in my opinion, are great in the first six weeks. In early childhood these procedures offer an opportunity to avoid irreversible bronchiectasis.

These criticisms are prompted by the authors' apparent lack of a full appreciation of the early diagnostic signs in young children, as I see it, when this disease most commonly starts. After watching many children with and without postural drainage and bronchoscopic aspiration, I am thoroughly convinced that, in early stages, bronchiectasis is frequently prevented. At the Children's Memorial Hospital, in the last twelve years, rarely has a properly treated case reached a hopeless ectasia. Without the X-ray and clinical signs of atelectasis, this stage of the disease would not be recognized. This early stage deserves more attention. This prophylactic treatment in the hands of an experienced bronchoscopist has no mortality and early recovery is possible. Surgery should be reserved for the unsuccessfully treated, neglected or overlooked cases.

This book, a brief modern history of bronchiectasis, covers the field of bronchiectasis in an altogether splendid manner and easily rates first among books on this subject. The authors are to be congratulated on their clear concise presentation.

Rehabilitation of the War Injured. A Symposium. Edited by William Brown Doherty and Dagobert D. Runes. Pp. 684, Philosophical Library, New York, 1943, cloth, $10.00.

By SAMUEL STANDARD

The late Dr. Seth Hirsh exhibited a piece of sculpture which he entitled "Cured, Discharged." It is a figure of a man in a battered felt hat, somewhat stooped, his clothes a little crushed, his face thin, worn and anxious, carrying a small bundle of his belongings under one arm as he leaves the hospital door.

Too often in our hospital experience the mere fact that a patient steps out of the hospital door is taken to mean that the medical profession has completed its job and that the patient is ready for return into his social environment. In most instances this error constitutes a shortcoming in medical care which emphasizes the disease and forgets the man that hangs around the disease.

The book entitled *Rehabilitation of the War Injured* is a symposium containing articles covering many fields of medicine. The major portion of it is devoted to reconstructive plastic and orthopedic surgery, the importance of physiotherapy, occupational therapy and vocational guidance following the treatment of the acute disease. A chapter is devoted to psychiatric and neurological problems encountered in the war injured.

Most of the details of operative procedures have been carefully chosen from the recent surgical literature and are intelligently put together in one volume from which a general surgeon, an orthopedist or a plastic surgeon could find much that is new and interesting.

The main contribution of the book, however, is the point of view which stresses the need for care by the patient who has had a recent illness. R. Watson Jones, whose knowledge and writings in the field of fractures have few superiors, devotes a chapter not to the care of fractures but rather to the rehabilitation of the patient after the fracture is healed. One example is worth repeating even in this short review. It is that of an air gunner in the Royal Air Force who, in November, 1940, was operated on for a torn and displaced semilunar cartilage. The wound healed without complications. There was no infection, no arthritis. "Despite daily treatment in the massage department, and two manipulations under anaesthesia to increase the range of motion, the muscles remained wasted and weak, the gait was slow and hesitant, the medical officer blamed him because 'he would not cooperate' that he was disinterested. This was his state in August, 1941, ten months after his operation. He was transferred to one of the orthopedic rehabilitation centres, he saw the sky, the sea and open spaces instead of the stone walls of the hospital, the stone walls of the massage room and the stone walls of the corridors. There was a lounge, a writing room, tasteful decorations, flowers, a menu which was varied and an atmosphere of well being and contentment. He learned to walk and then to run. He became an enthusiast and worked hard. He worked in the gym, played in the fields, swam in the pool, cycled on the track. In seven weeks he returned to his unit and to field duty. Ten months—total incapacity; seven weeks—full recovery." This story is encountered over and over again emphasizing the importance of the environment in which the patient lives, the relation of the patient to his local injury as well as care of that local injury.

In reading some of the details in surgical care there is a uniformity of emphasis laid upon the importance of the first treatment the patient receives. In head injuries, in major fractures, in skin avulsions, in jaw reconstructions emphasis is laid on the subsequent grief or subsequent joy that the first treatment will impose upon the patient. The importance of teaching men with little experience not the intricate details of complex surgery but the simple experience by which they will do no harm. Throughout the various well written articles in the book there is the constant repetition of the fact that if only no harm is done that in itself is an achievement.

The need for such a book and the excellent way in which this need is met prove beyond doubt the importance of mature sound judgment in planning the initial and subsequent treatment of the war injured. Such judgment must come by the process of accretion—knowledge built on previous knowledge. There seems to be no substitute for practical experience in the long-term care of the injured. The hour spent in the operating room is a part but only a part of the total care of the patient. The mechanics of operating is one thing, the field of surgery is

another. This book covers all the phases in the care of sick people with a lesser emphasis on the repair of diseased organs and on the immediate details of operative procedure, although these, too, are well covered.

The point this book drives home to the physician is the essential understanding that his contribution to the recovery of a patient is only one aspect of a complex problem. He must realize that the physician, the surgeon, the psychiatrist, the physiotherapist, the occupational therapist, the social service worker must all focus their varying intelligences upon the one central point—the bed-side, and later the convalescent patient. And they must bring to this a realization of the patient's reaction to his own illness, of his relationship to his environment, the social structure in which he lives and finally the relationship between that society to this, its temporarily injured member.

The book is recommended for all the reasons mentioned above. It should be read by physicians in all specialties and should be recommended as good reading for the medical student who will find in it a true orientation of the duties of a doctor to his patient.

Manual of Industrial Hygiene and Medical Service in War Industries. Issued under the Auspices of the Committee on Industrial Medicine of the Division of Medical Sciences of the National Research Council. Prepared by the Division of Industrial Hygiene, National Institute of Health, United States Public Health Service. A composite book with 16 contributors. Edited by William M. Gafafer. Pp. xi + 508, with 20 illustrations, W. B. Saunders Company, Philadelphia and London, 1943, cloth, $3.00.

By LEONARD GREENBURG

The rapid development of industrial hygiene makes this manual a most timely contribution.

The volume is divided into three parts: (*1*) Organization and Operation of Facilities, including medical and dental services; (*2*) the Prevention and Control of Disease in Industry; and (*3*) a discussion of the Manpower Problem. In all, there are some 24 chapters prepared by 16 authors, practically all officials of the U. S. Public Health Service.

The book is not intended to be, nor is it, a reference work on the occupational diseases, since but relatively few pages are devoted to the occupational diseases from a medical viewpoint; in fact, only some 20 pages are really devoted to this subject, exclusive of the dermatoses. The subject of the occupational dermatoses is perhaps one of the most complete chapters of the book. Other chapters which should be mentioned as being especially valuable relate to the engineering control of air contamination and certain aspects of plant sanitation, along with heating, ventilation and air-conditioning.

In mentioning these few more outstanding chapters, the writer does not desire to indicate that the remaining chapters in the volume are not crowded with interesting and valuable information. The book, viewed from the broader

viewpoint of the industrial hygienist, represents a fundamental landmark in the field, which should be read both for its factual content and its implications on the future of industrial hygiene.

MARGUERITE F. HALL: *Public Health Statistics. Pp. xxii + 408, New York, Paul B. Hoeber, 1942, $5.00.*

By GEORGE WOLFF

There are many textbooks on statistics, but only very few are especially written for the use of the medical man. This new book will prove to be a very helpful tool for the physician and public health officer who intends to employ statistical methods in research and administrative work alike. It is simply written and does not expect a great deal of mathematical knowledge which so often in a scientific guise conceals the lack of fundamental essentials and facts. "A great deal of stress has been given to the interpretation of statistical data," the author writes in her preface, and later in the introduction (page 17): "The final step in the statistical process is the analysis, generalization and interpretation of the data. This final step, which is the highest level in statistics as a method, involves a thorough understanding and appreciation of the field in which the statistics are being applied." These words should be underlined. It is only too frequently overlooked that without knowledge of the subject matter, in this case of basic pathology, the collection of statistical data remains a dead edifice, a graveyard of figures. The physician in most cases does not have the statistical knowledge desirable, any more than the statistician has the medical understanding. This book can really help to bridge the gap between both parties. Beyond question, it is necessary to learn the statistical technique which is by no means a difficult task if one follows a guide like the present textbook. The usual methods are described in detail: preparation of tables and graphs, collection and estimates of population data, the meaning of a standard population, the computation and evaluation of mortality and natality rates, crude, age-specific and standardized rates. A special chapter is devoted to the construction of a life table. And, of course, the foundations of statistical theory are not omitted; the theory of probability and the normal curve, the measures of central tendencies (mean values), of variability and correlation are discussed at hand of simple examples as well as the measures of reliability, error theory and chance variation. There is in this chapter a good and easily understandable table showing the formulae for the standard errors of the most important constants to be computed in statistical investigation. All this is done with a minimum of mathematical formulae, but with a good deal of explanatory text and examples mostly taken from some recent data in public health work. The mathematical derivations of the formulae are not given. Thus the book will indeed answer the needs of many medical workers who are looking for a guide in statistics; however, it is never superficial or deceiving the reader about the medical nature of the problems involved in public health. Those who want to go into the depths and details of the mathematical

theory will easily find for this purpose an additional textbook of a more mathematical character, of which many have been published before this.

Brief Comment

ERICH URBACH: *Allergy. With the collaboration of Philip M. Gottlieb. Pp. xxii + 1073, with 400 illustrations and 80 tables and charts, Grune & Stratton, New York, 1943, fabrikoid, $12.00.*

This is a work of near "handbook" dimension, both in regard to actual size and to completeness, including some 2,300 literature references. In the first part of the book, some 280 pages, the "Fundamentals of Allergy" are discussed. This comprises a full discussion of the theoretical aspects and the relations to other immunological processes and, what the author calls, nonallergic pathergy. Diagnostic and therapeutic principles of allergic diseases are here discussed, as well. The second part is concerned with the aetiological agents of allergic diseases. In the third part the individual disease entities are presented, grouped according to organ systems. Throughout this work, the rich experimental and clinical experience of the author is evident. There are 400 well chosen illustrations, most of which are a real credit to the publisher for the excellence of their reproduction.

Books Received

ITAZIL BENICIO DOS SANTOS: Rádio-semiologia da cisura oblíqua do pulmao. Pp. 114, with 41 figures, Biblioteca de Tisiologia do I. B. I. T., No. 1, Bahia, Brasil, 1942, paper.

MANOEL EZEQUIEL DA COSTA: Da Estratigrafia na Tuberculose Pulmonar. Pp. 88, with 35 figures, Biblioteca de Tisiologia do I. B. I. T., No. 2, Bahia, Brasil, 1942, paper.

WILEY D. FORBUS: Reaction to Injury. Pathology for Students of Disease Based on the Functional and Morphological Responses of Tissues to Injurious Agents. Pp. 797, with 532 illustrations, 20 of which are in color, Baltimore, The Williams & Wilkins Company, 1943, cloth, $9.00.

IAGO GALDSTON: Behind the Sulfa Drugs. With a preface by Perrin H. Long. Pp. 174, D. Appleton-Century Company, New York, London, 1943, cloth, $2.00.

Family Nutrition. Published by the Philadelphia Child Health Society, 311 South Juniper Street, Philadelphia 7, Pennsylvania. Pp. 119, paper, fifty cents.

The Hospital in Modern Society. Edited by Arthur C. Bachmeyer and Gerhard Hartman. Pp. xiv + 768, New York, The Commonwealth Fund, 1943, cloth, $5.00.

Publicaciones del Centro de Investigaciones Tisiologicas. Volumen VI. Director: Prof. Roque A. Izzo. Pp. 543, Pabellon "Las Provincias," Hospital Tornu, Buenos Aires, 1942, paper.

Tuberculosis in the United States. Graphic Presentation. Mortality Statistics for States and Geographic Divisions by Age, Sex and Race. Prepared by the staffs of the Division of Public Health Methods, National Institute of Health, and the Tuberculosis Control Section, States Relations Division, U. S. Public Health Service, under the direction of Carroll E. Palmer, M.D. Medical Research Committee, National Tuberculosis Association, 1943, paper.

Untapped Manpower. Facts and Figures on Employment of the Physically Handicapped. Pp. 15, United States Civil Service Commission, Washington, D. C., August, 1943, paper.

AMERICAN TRUDEAU SOCIETY

Report of the Committee on X-ray Apparatus and Technique

Dr. Ezra Bridge, *Chairman pro tempore*
Dr. Gilberto S. Pesquera, *Chairman in absentia*

Mr. Jean Kieffer	Dr. Homer L. Sampson
Dr. D. O. N. Lindberg	Mr. S. Reid Warren, Jr.
Dr. F. Maurice McPhedran	Dr. William Weidman

Our Chairman, Dr. Gilberto S. Pesquera, was granted a leave of absence from the first of 1943 to enter the Army. President Henry C. Sweany, M.D., appointed Dr. Ezra Bridge to the vacancy *pro tempore*.

The entire Committee met October 7, 1942, in New York City. The following ten subjects were considered:

(*1*) Laminography or planigraphy of the lungs can be completely evaluated only by comparison with Potter-Bucky roentgenograms made in the antero-posterior as well as in the postero-anterior position. The planigram is often indispensable in defining cavities, particularly those in dense, confused and obscured fields, and then it gives essential information that the Bucky wholly misses. Nevertheless, in the great majority of cases the Potter-Bucky technique will give decisive information, and in most cases is superior in defining the maximum limits of a cavity. In laminography a narrowed diaphragm is particularly desirable to reduce scattering and sharpen the image. (Project of Dr. F. Maurice McPhedran)

(*2*) By a combination of body-section roentgenography and object-film distances it is possible to determine definitely the size of cavities, foreign bodies and cardiac silhouettes within the thorax. (Project of Dr. Gilberto S. Pesquera)

(*3*) Stereoscopy as applied to chest roentgenography is often unsatisfactory, owing to improperly designed viewing apparatus and inadequate exposure technique. For the best stereoscopic effect the roentgenograms should be viewed the way they were taken. In the study of chest films there are wide limits in the relations between the tube shift, focus-film distance and stereoscopic viewing distance that are of value in practice. These relations have an exact physical basis for each object-film distance. This is the foundation of exact recording lesions and of their perception. (Project of Dr. Homer L. Sampson)

(*4*) Trivision photography and its application to roentgenography as presented to the Committee by Mr. Douglas Winnek, a guest, developed considerable interest. This type of photography produces a stereoscopic panorama of the part selected and provides a method of measuring depth of position and size of the part under scrutiny. (Mr. Jean Kieffer with Mr. Winnek)

(*5*) To secure further improvement in chest roentgenograms, contact with organized X-ray technicians is desirable, either by scientific papers or by lecture. (Project of Mr. Jean Kieffer)

(*6*) A more precise standard of acceptable densities in the diagnostic areas

of chest roentgenograms should be developed and popularized. Such a standard will be of distinct help in determining whether the densities of a given film are within the best range for that patient with the apparatus available. (Project of Mr. S. Reid Warren, Jr.)

(*7*) Greater attention should be given to producing more comparable chest roentgenograms. As a help in stabilizing technique the copper-step tablet, which registers on the film different degrees of density, is recommended. The ultimate value of this tablet depends upon the desire of the laboratory technician to turn out films that are scientifically comparable. (Project of Dr. William Weidman)

(*8*) More general hospitals should examine by X-ray the chests of all patients admitted. This recommendation is supported by our study of twenty large general hospitals scattered throughout the United States. No special technique or apparatus is suggested. It is more important to have chest examination by X-ray accepted as a routine admission procedure. (Project of Dr. D. O. N. Lindberg)

(*9*) Printed reproductions of four 14″ x 17″ chest roentgenograms on the same patient showing good and bad techniques are being considered for distribution to the membership and to others. (Project of Mr. S. Reid Warren, Jr.)

(*10*) The 4″ x 5″ photoroentgenogram on single emulsion film and taken with stationary grid gives easily visible detail, requires no enlargement, does not have to be reduced for filing, is easily handled, has low cost and is being more and more extensively used by the Army and industry. The Committee endorses it as a method of mass surveys, but not to the exclusion of other apparatuses and techniques. (Project of Dr. Ezra Bridge)

Recommendations: (*1*) That the Committee develop new projects and explore further those under consideration. (*2*) That funds be provided for two meetings in New York during the coming year.

NOTICE

Prof. J. B. Morelli, Director of the Instituto de Tisiologia of the Facultad de Medicina of Montevideo, announces a postgraduate course in the Theory and Practice of Tuberculosis, to be held March 13 to 25, 1944.